

LIVING BONE

In Health and Disease

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To Our Parents,
Families and Teachers

With particular thanks to the two men
who nurtured the senior author in his
early orthopaedic studies

Dr George E. Bennett
Dr A. Bruce Cill

Preface

During the past 50 years much information has been accumulated on the dynamic structure and the function of bone. Orthopaedic surgeons have become increasingly cognizant of the necessity of understanding the biologic processes of bone. It is our belief that a presentation of the picture of living bone will suggest many clinical as well as research possibilities to the thoughtful surgeon and physician.

An example of this lies in the appreciation of how bone forms in lamellar fashion. Nonunion represents the formation of a circular seal at a bone end. The obvious conclusion then is that any surgical procedure for nonunion must go back beyond the start of the seal so that the pattern of normal lamellar bone growth can be resumed with the aid of adjuvant bone-grafting material.

Bone functions not only as a structural framework but also as an organ of the body acting and reacting to normal and abnormal conditions. Furthermore factors producing changes in bone may affect other parts of the body.

As another example of the application of basic scientific knowledge in clinical work, it is well known that immobilization and bedfastness associated with the treatment of major traumatic or pathologic fractures result in osteoporosis and an outpouring of the released calcium and phosphorus into the blood stream. The danger which is well known clinically of ectopic soft tissue calcification, particularly of the kidneys obviously is increased by any extra dietary intake of calcium, phosphorus and vitamin D. The logical therapeutic step of early ambulation in major fracture treatment is apparent. If ambulation is not possible it will be seen that the intake of calcium, phosphorus and vitamin D in bedridden patients should be kept at the lowest possible level so as not to add to the already excess material which must pass through the kidney parenchyma in such a patient. The additional use of magnesium carbonate for its effect on mineral solubility also may be suggested by our data.

The first part of this book is a consideration of the structure, the function and the reactions of normal living bone. There is included a detailed discussion of vitamins, minerals, carbohydrates, proteins, hormones and physical agents as these are related to bone. It is our hope that this basic material will be of value in assisting the physician and the surgeon to understand what makes bone a living organ of the body.

The second part is a presentation and a discussion of the more common derangements of the skeletal system as they are now known, with an attempt to catalog them according to basic mechanisms and manifestations. This also is done to point out the possible relationship and even the possible pathologic continuity between diseases that at one time may have been considered quite independent. The responses of living bone to the wide variety of normal and pathologic stimuli confronting it are somewhat limited. This has led to considerable confusion regarding the proper differentiation of various bone lesions. For example in the rickets group it is now possible to differentiate a large number of disease entities. The pathologic, the roentgenographic and the clinical findings in many cases show a striking similarity but the mechanisms

responsible for each type are different and must be determined by further studies. Only after such studies have been made can rational therapeutic procedures be instituted.

In some instances diseases whose skeletal manifestations are only of secondary incidence have been included because at times they may present bone symptoms and require treatment. In the process of assembling these diseases the relationship between them began to fall into an orderly pattern resembling a "periodic table" of bone affections. This concept may well help the careful scientific worker to fill in the as yet unknown "elements." At present, a more practical classification is needed by the clinician. Consequently we have devoted Part Three to a method of classification accompanied by tables. The roentgenographic tables list lesions that, on roentgenographic study are localized disseminated or generalized, each of these in turn being subdivided into bone-absorptive bone-formative or mixed lesions. These tables will allow the clinician confronted by a given clinical, roentgenographic or blood-chemical finding to proceed in an orderly comprehensive manner to assemble the clues necessary for final diagnosis and management.

This book, it is hoped will be of interest to the student for an over-all picture of bone and bone diseases and to the laboratory worker as a correlation of his chemical studies with clinical and x ray findings. The roentgenologist will find a juxtaposition of roentgenograms with clinical and laboratory data. The clinician will note a collection of clinical chemical x ray and pathologic material as well as methods of treatment indicated or suggested by the information at hand. Surgical therapy has been discussed in detail where indicated.

Research and therapy both have been presented in the light of past accomplishments and future possibilities. It is only in this way that work in these fields can go forward.

The senior author never would have envisioned this work without the stimulus and the opportunity given to him by his teachers and associates. His earliest work in bone metabolism was encouraged by Dr. George E. Bennett and Dr. A. Bruce Gill. These pioneers in modern orthopaedic surgery realized that bone was not an inert substance. It was they who provided for study the early cases of Paget's disease, von Recklinghausen's disease, myositis ossificans progressiva and other bone diseases including varying forms of rickets. An appreciation of the orthopaedic surgeon as a scientist rather than as a bone carpenter was gained through contact with these men. An understanding of bone pathology was obtained by the senior author from Dr. Charles F. Geschickter and by the other authors from Dr. Henry L. Jaffe. Dr. Mitchell I. Rubin was of great aid in the appreciation of biochemistry in relation to bone and the detailed biochemical work of both blood and balance studies, was done by Dr. Lasko Kajdi and Dr. E. P. Corson-White.

We wish to thank Dr. Maurice M. Pomeranz and Dr. Eugene P. Pendergrass for many unusual roentgenographic illustrations. Dr. Philip J. Hodes aided in the analysis of some of our bone roentgenograms. Thanks also are due to Dr. Fritz T. Callomon for his valuable assistance with the bibliography and his expert translation of many articles from foreign literature.

We particularly thank Walter Kahoe, J. Brooks Stewart, Stanley A. Gillet and Laura E. Moore of the J. B. Lippincott Company for their expert counsel and help.

Preparation of the manuscript was ably performed by Mrs. Eleanor C. O'Donnell and Miss Barbara S. Leick transcribed the captions.

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PART ONE

Living Bone in Health

Bone and Its Structure

INTRODUCTION

The field of investigation of bone and cartilage is a constant challenge. Much has been done and many research workers have left their names indelibly attached to now familiar gross and microscopic structures. What were research data without practical connotation yesterday are important and useful facts today.

Each time something additional about bone or cartilage is learned new problems arise which often demand new modalities of investigation. Originally there was gross anatomy and then came microscopic anatomy with conventional and later special stains. Now there have been added studies by polarized light x-ray diffraction and electron microscopy.

Both bone and cartilage are complex differentiated connective tissue. They are a mixture of organic material and intercellular substance. Bone is unusual in that it is impregnated with minerals; cartilage in that it is in a gel state and also may be impregnated with minerals.

Bone as a mineral impregnated substance is difficult to study because of the firm union of the mineral to the organic portion. At present one cannot remove one component without affecting the other. It would be ideal if detailed histologic chemical, physiologic, crystal and mechanical observations could be made on intact living bone. The efforts of all research workers have been directed toward this goal.

Early investigations involved study of bone sections made thin by grinding—material that is dead tissue but useful to demonstrate the calcified framework of bone. Next decalcified fixed sections of bone re-

vealed some cellular detail. Further interesting findings resulted from studies of microscopic sections prepared by cutting fixed undecalcified young bone. Then the inorganic mineral content of bone was determined by chemical analysis of bone ash.

As new modalities of study come into being other approaches were possible such as x-ray diffraction studies for crystal structure and electron microscopy of finely ground pieces for minute organic and inorganic structure.

Studies of living metabolizing bone have been carried out by tissue culture and by the use of tracer substances. At present, these tissue cultures can be done only upon cartilage and young bone. It is to be hoped that similar dynamic investigations ultimately can be carried out on adult bone.

Since cartilage and connective tissue are easier to investigate than bone, much more information has accumulated about them. Cartilage plays a role in bone formation. Connective tissue enters into the formation and the structure of bone. Much of our information about bone has been interpolated therefore from studies of these structures.

STRUCTURE OF CARTILAGE

Cartilage consists of a dense mesh of collagen fibers incorporated in a condensed, amorphous intercellular substance. This complex structure is smooth and resilient. There are three types of cartilage all basically alike but differing in the proportion and the type of fiber structure. These are fibrocartilage, elastic cartilage and hyaline cartilage, the last being the prototype.

Fibrocartilage is a highly differentiated

structure specifically adapted to supplying great tensile strength at tendon insertions. It is unique in relation to the other two forms in that its intercellular substance contains excess collagen arranged in fibers parallel with the tension placed upon it (Fig 1) This type of cartilage also forms as a repair response to hyaline cartilage injury. It forms the intervertebral disks, the pubic symphysis and the interarticular menisci (clavicle, sternum, jaw and knee). It is found also in the glenoid and the cotyloid ligaments and in the ligamentum teres of the femur.

Elastic cartilage is found in the eustachian tube, in the epiglottis, in the external ear and in some of the laryngeal cartilages. Its structure is similar to that of hyaline cartilage except for the fact that it contains large amounts of elastic fibers (Fig 2).

Hyaline cartilage is the most important form as it is widely distributed in the body. It also is the fetal and the early childhood anlage of much of the skeletal system. It forms the articular cartilages, the costal

ELASTIC FIBERS IN
INTERCELLULAR
SUBSTANCE

CARTILAGE CELL

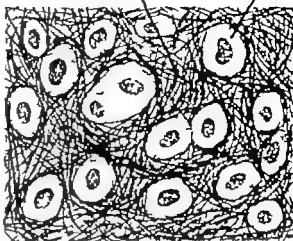


FIG 2 Elastic cartilage. The cartilage-cell nests lie in a matrix containing large numbers of elastic fibers.

cartilages and the cartilages of the nose and the laryngotracheobronchial tree. With the exception of the small differences mentioned above, the composition of hyaline cartilage

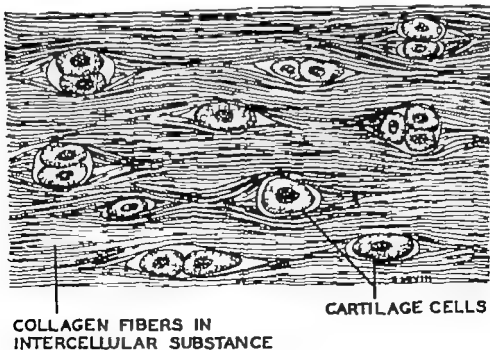
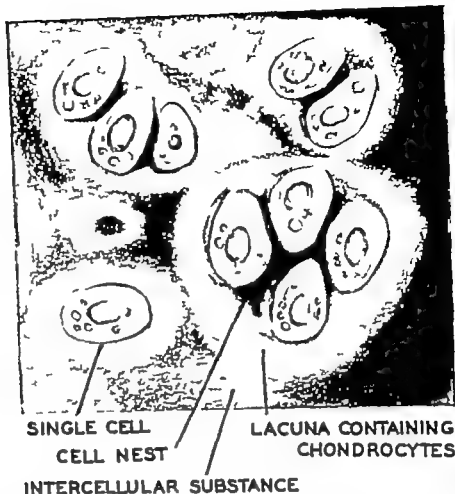


FIG. 1 Fibrocartilage. Groups of cartilage cells in a matrix of fibrous connective tissue.

FIG. 3 Hyaline cartilage. The cartilage cells lie singly or in clumps in the lacunae. The intercellular substance is homogeneous and basophilic.



is typical of all cartilage (Fig. 3). Hyaline cartilage is composed of cells and intercellular substance. These cells are known as chondrocytes. The mature cartilage cell lies in a lacuna or space in the ground substance. A lacuna may contain one or at times more than one cartilage cell.

The intercellular substance of cartilage consists of collagen fibers bound together with cement substance (Fig. 4). The collagen fibers are formed from linked polypeptide chains. The collagen fibrils are joined together by a mucopolysaccharide cement substance which is probably chondroitin sulfuric acid.

No capillaries touch cartilage cells directly as they lie in their lacunae surrounded by matrix (Fig. 3). Cartilage structure is bathed in tissue fluids, and nutrition can reach the cell only by diffusion through the matrix.

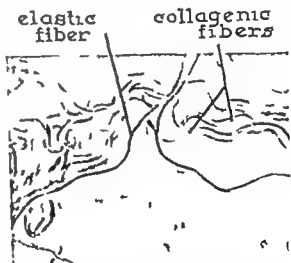


FIG. 4 Collagenic and elastic fibers as seen in a fresh, unstained, teased preparation of areolar tissue with the light cut down. The elastic fibers are more refractile than the collagenic. (From Ham A. W. Histology ed. 2 p. 191 Philadelphia, Lippincott, 1953.)

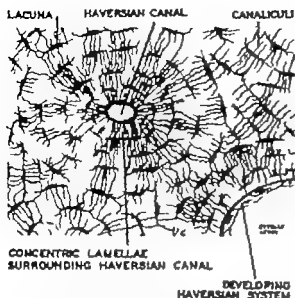


FIG 5 Cross section of the Haversian systems. Schematic drawing of dried uncalcified bone. The lacunae are shown as black-colored areas with radiating lines representing the canaliculi

Except at joint surfaces cartilage is covered by perichondrium. Like periosteum this may be separated into two layers—the outer is a fibrous one while the inner is a more primitive cellular part. The inner layer represents a source of continued cartilage cell formation.

DEVELOPMENT OF CARTILAGE

Cartilage develops in the fetus from the mesenchyme whose cells differentiate into chondroblasts and lay down the matrix. The chondroblasts hypertrophy to form the chondrocytes which are the living cells of hyaline cartilage. Chondrocytes also may produce phosphatase and die as coincident calcification of the cartilage occurs.

Once differentiated cartilage grows in two ways—by interstitial and by appositional growth.

1 Interstitial growth is represented by the division of chondrocytes. This can occur only in the young subject with plastic inter-

cellular substance. The cartilage expands in all directions like the foam of a detergent when it is mixed with water.

2 Appositional growth occurs from the inner layer of the perichondrium. It infers growth by the addition of new cartilage that is laid or apposed upon the old (hence the term appositional). This is the type of growth observed in cortical bone formation and in mature hyaline cartilage.

STRUCTURE OF BONE

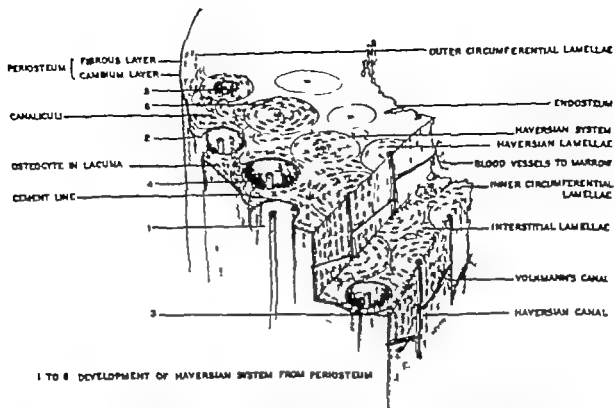
All bone is composed of a combination of organic and inorganic material. It occurs in three structural forms designated as cortical, cancellous and medullary. All three structural forms are present in varying degree in every bone. Cortical or compact bone composes the hard surface layer of all bone. It varies in thickness in different bones. The cancellous and the medullary bone are found internal to the cortical bone.

CORTICAL OR COMPACT BONE

Compact bone often is referred to as cortical bone but for purposes of describing its intrinsic structure the term compact bone is preferable. It is a dense lamellar structure. This means that it is arranged in thin layers. These layers are a three-dimensional system (Fig. 6). In a typical long bone they may be described as follows:

There are multiple parallel longitudinal channels known as Haversian canals, which carry blood vessels, lymphatics and nerves. Surrounding the central Haversian channel are a varying number (from 8 to 15) of concentric lamellae or rings of bone. The lamellae plus the canal and its contents are called a Haversian system (Fig. 5). The canals run from metaphysis to metaphysis in a longitudinal direction; the concentric lamellae encircle each tube in a circular manner.

Subperiosteally and subendosteally. In addition lamellae are laid down in ringlike fashion for several thicknesses. These lamellae are known as outer and inner circumferential lamellae respectively. They en-



1 TO 6 DEVELOPMENT OF HAVERSIAN SYSTEM FROM PERIOSTEUM

FIG 6 Three-dimensional diagram showing a composite cross section and a longitudinal section of the shaft of a long bone (after Ham). The relationship of the Haversian and the Volkmann canals to the periosteum and the endosteum is depicted. In addition the development of a Haversian system by the conversion of a trough on the periosteal surface of the bone into a longitudinal tunnel surrounded by concentric lamellae is shown as stages 1 through 6

circle the entire shaft of the diaphysis in the subperiosteal and the endosteal areas

Lying between Haversian systems are the interstitial lamellae. These actually represent the remains of previous Haversian systems in addition to the remnants of outer circumferential lamellae. Interstitial lamellae are the result of absorption of bone by the remodeling process.

The Haversian systems run longitudinally and roughly parallel with each other. They are connected transversely by tubes referred to as Volkmann's canals (Fig 6). These canals are not surrounded by concentric lamellae because concentric lamellae only form to encircle the longitudinal axis.

It is thus obvious that tubular bones are constructed principally in the longitudinal axis. This resists transverse forces. Resist-

ance to forces in other planes is supplied by the integrated cancellous bone.

CANCELLOUS BONE

Cancellous bone is continuous with the inner surface of cortical bone and exists as a three-dimensional lattice of bone trabeculae. In the case of long bones the spaces within this lattice are continuous with the medullary cavity. In other bones the cancellous lattice is the principal internal structure. The spaces between the lattice projections are simply compartmented marrow cavity. The contiguity of this bone to blood and marrow spaces obviates the need for Haversian systems in the cancellous bone.

MEDULLARY BONE

Actually this is largely the marrow cavity.

ity which is continuous with the inner surfaces of the cancellous bone. It is simply a nontrabeculated expansion of the central area of tubular bones. It is filled with marrow and reticulum cells as well as blood and lymph vessels.

PERIOSTEUM AND ENDOSTEUM

There is no such thing as naked bone. Bone is covered on both the outside and the inside with specialized connective tissue according to its location called either periosteum or endosteum. The periosteum is the outer surface covering generally consisting of two layers. The outer layer is fibrous and relatively acellular and is termed the fibrous layer. The inner layer which is called the cambium layer is densely cellular. These layers of connective tissue have cellular elements present in varying forms of differentiation. Under proper conditions the primitive cells of these structures develop into bone cells. The endosteum is a single layer of connective tissue that is cellular. It is therefore similar in form and function to the inner layer of the periosteum.

CIRCULATORY SYSTEM

Since all cellular elements of bone are living they require a circulation to take care of their needs in regard to nutrition and the removal of waste products.

Blood reaches all bones through the periosteal vessels. The long bones are each supplied in addition by the nutrient artery. The nutrient artery which runs in the nutrient canal originally penetrates the cortex of the midshaft at right angles. With growth its direction becomes oblique. This is because in the lower extremity growth of long bones is greater at the knee whereas in the upper extremity it is greater at the shoulder and the wrist. The nutrient artery pierces the shaft to reach the medullary canal where it branches into ascending and descending branches. These branches terminate in sinusoidal capillaries. The nutrient artery on its way through the bone con-

nects with the blood vessels of the haversian systems.

Since bone is a rigid structure, a network of tunnels is required for circulation. These haversian and Volkmann's canals are located in a three-dimensional lattice (Fig. 6). The former run longitudinally, the latter run transversely. They all interconnect with each other and with the vessels of the periosteum, the epiphyseal areas and the marrow sinusoids. The tunnels that run in the cortex in a longitudinal direction are the haversian canals. Those running in other planes are Volkmann's canals. These are the interconnecting tubes.

Haversian canals start as troughs on the surface of cortical bone (Fig. 6). As cortical bone develops in layers by lamellar apposition these troughs become roofed over and are transposed into tubes which contain central vessels, lymphatics and a little fatty tissue.

Volkmann's canals are intercommunicating or penetrating tubes. These are not surrounded by lamellar layers but run in the interstitial areas between the haversian systems (Fig. 6). In this way they interconnect the haversian systems.

The fundamental purpose for this circulation is to supply the osteocyte. Thus lies in its lacunae and its cellular processes extend into the canaliculi (Fig. 5). The canaliculi interconnect with those of adjacent osteocytes.

This osteocyte and its processes in the branching canaliculi are bathed by interstitial fluid. This fluid in turn exchanges by diffusion with adjacent capillaries and lymphatics of the haversian systems.

NERVES

Certain areas of bone, notably the periosteum and the endosteum, carry somatic afferent fibers.* Bone also responds to the autonomic system. Because of its relative indestructibility in relation to other struc-

The pacinian sensory bodies are found in the periosteum. Little is known about nerve endings in the bone itself or in the marrow.

tures at times the response may appear paradoxical. Nevertheless it does respond and this presumes autonomic fibers possibly carried in the vessel walls.

BLOOD-FORMING ELEMENTS

In discussing soft tissue elements of bone one cannot ignore the hematopoietic and the reticuloendothelial systems contained primarily in the marrow. Affections of these produce changes in the bone structure. Examples are the changes seen in Mediterranean anemia, Hand-Schüller-Christian disease, Letterer-Siwe disease and the like.

Under normal conditions the marrow shifts from a hematopoietic to a fatty type after 5 years of age in many locations. It may shift further to a fibrous marrow seen in certain disease states as in Paget's disease.

In the first 6 years of life the marrow is nearly totally red and cellular. Between the ages of 5 and 7 a slow transposition to fatty marrow occurs. The pattern is the appearance of fat cells which gradually replace the red cellular marrow. The replacement starts at the distal portions of the skeleton and proceeds toward the trunk.

By the age of approximately 18 years active hematopoietic marrow remains only in the following areas: (1) vertebrae, (2) ribs, (3) sternum, (4) skull, (5) pelvis, (6) proximal epiphyses of femur and humerus.

It is interesting that research¹ indicates that temperature plays a role in this replacement. When the temperature of the extremities in experimental animals was raised the hematopoietic tissue increased. It is felt, therefore, that the normal relative cooling of the distal portions of the skeleton accounts for the transition to fatty marrow in these locations.

DEVELOPMENT OF BONE

Embryologically bone may arise by endochondral, membranous or mixed formation. The multipotential primitive connective tissue cell is embryologically significant in

the development of the precartilaginous mold. It will be discussed in detail later.

ENDOCHONDRAL BONE FORMATION

In the scale of evolution the elasmobranchii (sharks, dogfish and the like) are the highest forms which have skeletons entirely of cartilage. For such creatures which are aquatic, weight bearing is not a problem. But in higher vertebrates cartilage is not sturdy enough for a skeletal structure. Calcified cartilage is not satisfactory either because calcification of cartilage matrix interferes with diffusion of nutrients to the cells. When cartilage calcifies the chondrocytes die and the intercellular substance produced by those chondrocytes melts away.

Nature therefore has devised a most ingenious method of developing an adequate skeleton. It evolves a mold of cartilage which is in the form but not the size of the ultimate adult bone structure. This holds true for all bone except the vault of the skull, the clavicle and the mandible. This cartilage anlage of future bony structure is a temporary skeleton. It forms and then is replaced by a duplicate in bone (Fig. 7). This method is referred to as endochondral bone formation.

Progressive calcification of the original cartilage mold precedes absorption of the calcified cartilage by chondroclasts (Fig. 7). Simultaneously with the absorption of the calcified cartilage, connective tissue cells capable of differentiating into osteocytes infiltrate this mold (Fig. 7). These cells originate from an enveloping primitive connective tissue sheath called the perichondral splint.

The cartilaginous pattern of the final bone form is thereby converted into bone. This is the method of formation of the diaphysis of all bones formed by the endochondral method. This process begins *in utero* and continues until full conversion to bone occurs.

Cartilaginous areas remain at the ends

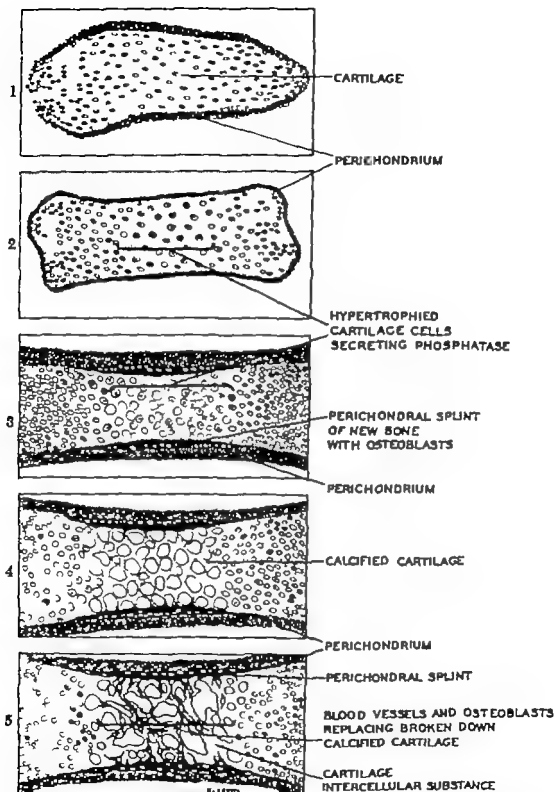


FIG 7 Development of diaphysis of a long bone showing perichondral splint (1) cartilage anlage (2) cartilage-cell hypertrophy with secretion of alkaline phosphatase by mature chondrocytes. (3) initial transformation of perichondrium into osteoblastic tissue at periphery of diaphysis, (4) calcification of cartilage cells accompanied by their necrosis, (5) the final stage of osteoblastic and capillary invasion of the centrally placed dead and dying chondrocytes originates from the peripheral perichondral splint.

of long bones throughout the growth period of the individual. These are the areas in which longitudinal growth takes place. These are the epiphyseal centers and the epiphyseal plates (Figs. 8-9).

Near the middle of an epiphyseal center at a time appropriate for each particular location cartilage calcification occurs. This is closely followed by capillary invasion and bone replacement. The source of this capillary invasion of an epiphyseal center with subsequent ossification is not understood clearly.

The epiphyseal plate remains as cartilage throughout the growth period. Indeed were it not for the ever present proliferating cartilage-cell zone here longitudinal growth could not progress.

To repeat, bone in itself can grow only by apposition. If increase in length occurs

it can come only from proliferation of cartilage cells at the epiphyseal plate and the replacement of these cartilage columns by bone (Figs. 8-9).

In endochondral bone formation chondrocytes hypertrophy and produce phosphatase. Increase in glycogen in the cytoplasm of the chondrocyte then occurs. Shortly thereafter calcification of the cartilage matrix takes place. At this moment the increased glycogen disappears.

It has been recognized for many years that alkaline phosphatase catalyzes the liberation of organic phosphorus. This makes this element available for matrix calcification. More recently, the source of the organic phosphorus has been shown to be a phosphorylative glycogenolysis which requires the enzyme phosphorylase. This process appears to be related to the hypertrophy

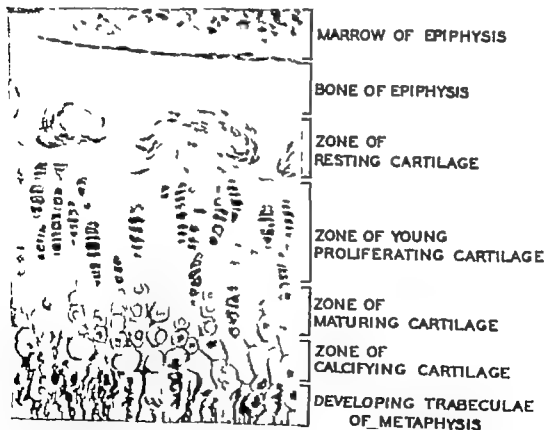


FIG. 8 Epiphyseal plate (after Ham). The zones of cartilage cell at the epiphyseal line are shown in the course of their participation in the process of endochondral bone formation.

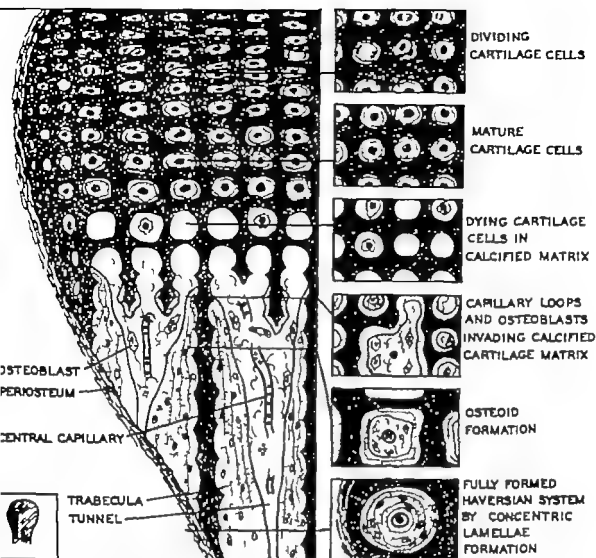


FIG. 9 Epiphyseal plate and metaphysis of a long bone. Composite cross section and longitudinal section (after Ham) The zones of resting proliferating and calcified cartilage are shown. Capillary loops and osteoblasts invade the dying cartilage to form metaphyseal bone trabeculae. The central trabecular capillaries become surrounded by concentric bony lamellae and thus haversian systems are formed.

of the chondrocyte and the increase of its glycogen that occurs just before matrix calcification. Under the control of the enzyme phosphorylase it is thought that hexose phosphoric esters are formed in the process of glycogen breakdown. These organic phosphorus combinations in turn serve as substrates for the liberation of phosphorus by alkaline phosphatase which acts only on organic phosphorus compounds. It is also in keeping with this theory that the glycogen

content of the cartilage cells disappears as matrix calcification occurs at the beginning of endochondral bone formation. This mechanism has been termed the "local factor" in calcification.²

When calcification of the intercellular substance has occurred nutrient materials, previously able to diffuse through the matrix in the form of crystalloids and gases no longer can penetrate the calcified matrix. As a result the chondrocyte dies and then

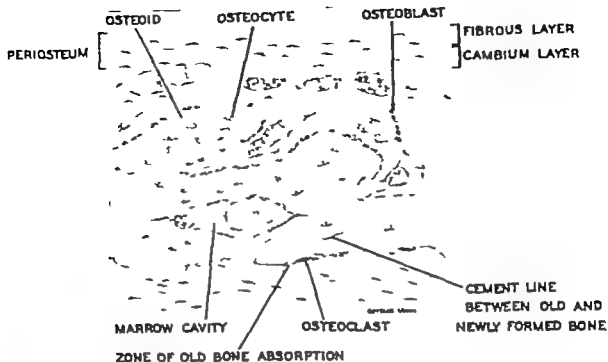


FIG. 10 Intramembranous bone formation in the fetal skull. Direct osteoid formation is brought about by osteoblasts in the proliferating stage. Simultaneous modeling of the bone trabeculae occurs in the presence of osteoclasts.

its matrix melts away but the mineral material is available to the ingrowing osteoid.

During this stage capillaries grow into the calcified cartilage structure bringing osteoblasts with them. The osteoblasts produce bone matrix and differentiate into nesting osteocytes. The primitive connective tissue about this structure further differentiates to form additional osteoblasts which are bone formers, osteoclasts which are bone modelers and osteocytes which are an integral part of formed bone.

INTRAMEMBRANOUS BONE FORMATION

In intramembranous formation the miniature of adult bone is in the form of a fibrous mold—e.g., the cranial vault. In this type of formation there is a direct transition of primitive tissue to bone through differentiation (Fig. 10). Longitudinal growth occurs in a continuous primitive tissue edge.

In mixed formation such as in the clavicles and in the distal phalanges of the fingers both types of differentiation occur simultaneously.

Mineralization occurs when minute calcareous areas appear in and among the osteogenic fibers as a result of alkaline phosphatase deposition. Indeed the presence of alkaline phosphatase appears to precede calcification.³ These areas fuse to form spicules of bone in which osteocytes are entrapped. The underlying chemical relationships in matrix formation and mineralization are similar in membranous and in endochondral bone formation.⁴

CELLULAR COMPONENTS OF BONE

Cellular components of bone are the osteoblasts, the osteoclasts, the lymphocytes and the final adult bone cells, the osteocytes (Fig. 10). Numerous histologists are of the opinion that one cell may differentiate into

another. All the cells arise from primitive connective tissue.

The osteocyte is the final adult bone-cell form. It has a life of many months. It is located in a shallow depression in the intercellular substance which is called a lacuna (Fig. 5). It interconnects with other osteocytes by processes which extend through tiny channels that are termed the canaliculi (Fig. 5). These cells are so highly differentiated that they have no reproductive ability.

The lymphocyte has a function in bone metabolism. Whether it serves to transport material to or away from bone areas is debatable.

The osteoblast is a form of connective tissue cell which may differentiate into either an osteoclast or an osteocyte. It has the capacity to produce intercellular substance or osteoid tissue. It is found in the periphery of new and old bone forms. Osteoblasts appear to be present universally when bone is being formed rapidly.

The osteoclast is vital in the shaping, the modeling and the clean up of bone. It has the capacity to break up bone osteoclasts

Up to this point the authors have presented facts about bone and cartilage that are basic and long understood. The following pages contain a summation of much new work on the submicroscopic structure and the formation of bone and cartilage representing largely investigative material. Some is quite clear and accepted; some is speculative; some will undoubtedly suggest new research pathways.

Cellular Function in Bone Formation and Destruction. An osteoblast takes 10 days to produce the amount of bone that can be destroyed by an osteoclast in 8 hours. As a matter of fact, an osteoclast can undo the work of several osteoblasts quickly. The life of an osteoclast appears to be about 96 hours, whereas the life of an osteoblast appears to be many months. It also appears at times that both osteoclasts and osteoblasts may form and model bone. However,

since these conclusions are from microscopic sections of investigative material, one can not be certain of the double actions of these two cells. The mere presence of an osteoclast where there is new bone does not necessarily mean that the osteoclast is participating in the bone formation. The mere presence of an osteoblast where there is bone being dissolved or eroded may mean simply that it is there to produce activity and reaction toward bone formation. Although it is possible that osteoblasts and osteoclasts can both form and destroy bone, it is still a reasonable working hypothesis to consider that the osteoblast is primarily for bone formation and the osteoclast is primarily for bone absorption.

Formation and destruction of bone are concerned with the same cells in different functional states. When bone is developing in marrow, the reticular cells are able to turn into osteoblasts and these, in turn, into osteocytes. When it is being destroyed either by parathyroid hormone in mammals or by the stimulus producing rapid changes during the egg-laying cycle in birds, the liberated osteocytes and osteoblasts form osteoclasts.⁸ These in turn can go back to osteoblasts or can settle down as reticular cells. Bloom⁹ reached this conclusion on the basis of study of rapid cellular transformation in birds in egg-laying cycle and after massive toxic injections of parathyroid hormone in animals.

The mechanism by which the osteoclast and in some instances the osteoblast destroy osteoid and mature bone is complex. It has been long known that parathyroid hormone may cause bone destruction possibly directly by stimulation of osteoclast formation. It has also been postulated that normal body fluids tend to wash out bone salts and that this is prevented by the presence contiguous to the bone surfaces of alkaline phosphatase. It has further been thought that if acidification is sufficiently high, bone substances will be washed away and eroded. In the past, the idea of halitosis has been considered—that is, a wash

ing out of inorganic material alone. Then came the swing-over to the thought that decalcification could only mean simultaneous dissolution of organic and inorganic bone substance. Now Hendricks' beautiful work on crystallography indicates that certain inorganic materials are not in the lattice of bone but outside upon the crystal surface.¹ This leads one to believe that a combination of both bone absorption and halisteresis may occur either together or singly.

The nature of calcified osteoid cartilage and mature bone is such that it is possible to postulate their destruction on the basis of such a dual enzymatic action.

Sizer has shown that stresses increase enzymatic digestion of tendon. It is possible therefore that stresses and strain in bone may also affect the enzymatic activity.²

The possible role of collagen-splitting enzymes and depolymerizing enzymes on bone destruction certainly may be studied further. In part the role of such enzymes may be an explanation for the changes occurring during the egg laying cycle in birds and in association with the parathyroid glands' action directly upon bone. It has been demonstrated clearly that sections of parathyroid placed in contact with bone under its fibrous covering will cause direct dissolution of bone substance. This dissolution of bone starts at the poles of the parathyroid graft. No cellular osteoclast activity need occur to produce this absorption of bone.³

The conclusion in regard to the role of cells in bone formation and destruction is that connective-tissue cells appear to be interchangeable. Only the osteocyte may be an end stage. Cellular interchange is regular site in bone formation and bone destruction. The *modus operandi* is not understood fully.

CARTILAGE AND BONE MATRIX

A truism frequently stated is that "the intercellular substance characterizes connective tissue." So bone is characterized by its

organic calcified matrix. The basis of the matrix is a collagen fiber produced by the osteoblast. Inorganic salts combine with this material. Integration of inorganic with this organic material changes the characteristics of the matrix. Most important this combination changes an uncalcified osteoid to a structure difficult to reabsorb into a calcified osteoid, a structure easy to reabsorb.

This union is of such a nature that usually the inorganic material cannot be washed out to leave organic structure. If reabsorption occurs then it usually is of both inorganic and organic material.

Lying between the cells of a paraffin section of cartilage one sees a homogeneous area which is bluish-staining with hematoxylin (Fig. 3). In this area are seen certain faintly staining fibers especially around mature cartilage cells. These are collagen fibers and can be demonstrated further by specialized techniques with enzymatic digestion (usually using saliva) followed by impregnation of the material with silver. These fibers are also demonstrated commonly by polarized light.

Electron microscope studies reveal these collagen fibers to have a banded appearance (Fig. 14). By means of a wide-angle x-ray diffraction the fibers observed in the electron microscope can be shown to be aggregates of polypeptide chains.⁴ The similar amino-acid content of collagens derived from skin, bone cartilage, etc., would indicate that these structures are closely related if not identical. Amino-acid pattern in collagen fiber protein is unique for the following reasons: (1) there is an extremely high (25 per cent) glycine content; (2) proline and hydroxyproline are found (approximately 30 per cent) and (3) hydroxyllysine is found only in collagen. Collagen lacks cystine and tryptophane and it has tiny amounts of tyrosine and methionine.

These facts are important in producing specific configurations of the collagen polypeptide chain. For instance the amino-acid residue length of 3.4 angstrom units will be reduced to 2.86 angstrom units when the

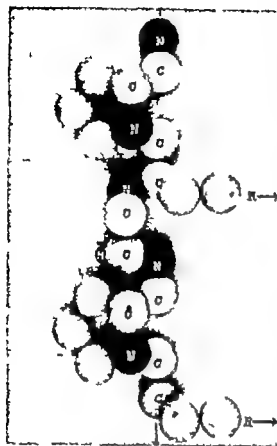


FIG. 11 The effect of imino acids on the fiber-axis spacing of a polypeptide chain. The proline-containing polypeptide chain has the fiber axis spacing reduced to 2.86 Å. A conventional amino-acid polypeptide chain has a fiber-axis spacing of 3.4 Å. (From Astbury N. T. and Bell F. O. Molecular structure of the collagen fibers. *Nature* 145:421)

Imino acids proline and hydroxyproline are present (Fig. 11)

Pauling¹⁰ has formulated a structure for the collagen fibril. He theorizes that it is comprised of 3 polypeptide chains bound together by hydrogen bonds. Each of these chains is coiled into a helix so that a cylindrical molecule is formed. These molecules are arranged as hexagons and form a fiber of tendon or of connective tissue. It is well conceded by workers in the field that the structure of the collagen fiber is not yet established. Each of the proposed structural configurations has been modified by subsequent work.^{10a}

The other component of matrix besides a specific collagen fiber is the interfibrillary material or the ground substance. This ground substance in cartilage is chondroitin sulfuric acid. It is a long-chain polysaccharide composed of residues of glucuronic acid and acetyl-galactose-amine-sulfuric acid. It is this polysaccharide which is considered responsible for the metachromatic properties of cartilage (Metachromasia is the taking on by a substance of a color different from that of the dye with which said substance is treated). When they are stained with toluidine blue sulfated mucopolysaccharides show a reddish color.

Many structural formulas for chondroitin sulfuric acid have been postulated but to this date no specific structure has been proved. There is undoubtedly a bond uniting the collagen fibril protein to the polysaccharide ground or binding substance. However, while the precise nature of this bond is not known, the hope is that eventually it will be clarified.

Like cartilage the organic component of bone which is called osteoid is made up of collagen fibers which show a typical periodicity of approximately 640 angstrom units. This means that each link in the collagen fiber chain is composed of a band. The length of a band is 640 angstrom units. The amino-acid pattern of bone is similar to that described above for cartilage and collagen in general.

Since it has been observed that cartilage may directly calcify intercellular substance eventually and form bone material it has been assumed that the underlying chemical problems are alike. The work indicated above in regard to the collagen-fiber structure and the polysaccharides has, of course, been done upon cartilage. What is true for cartilage has been inferred for bone.

The polysaccharide component of bone has not been studied extensively. It is not known for certain whether or not there is chondroitin sulfuric acid in bone. The question of the composition of bone matrix has been retarded tremendously by the presence

of lime salts. It can be postulated, however, that there is a basic collagen fiber structure and polysaccharide ground substance that is similar to that of cartilage. It is of interest, however, that the sulfate content of bone is lower than that of cartilage.⁴

It is considered that the mucopolysaccharide substance is found first in the osteogenic fibers. It then spreads throughout the osteoid tissue and becomes included in the cement substance of the matrix.⁴ This means that mucopolysaccharide as determined by the Hotchkiss method is only a part of the cement substance. This cement substance is between the collagen fibers and seemingly holds them together. It may be compared with the complex glue which binds sheets of wood together to form plywood. The sheets of wood may be likened to collagen fibrils.

The mechanism whereby the cartilage cell induces the formation of matrix is at this time obscure. Considerable work has been done upon this subject and is still in progress.

Certain data are available on bone-matrix formation. Ribose nucleic acid in the osteoblast is associated with protein synthesis and in addition phosphatase appears to be associated with elaboration of fibrous protein. However, it is also possible that cytochrome oxidase and/or glycogen are related to the production of the fibrous protein, the so-called matrix.⁶

Glycogen is distributed at first throughout the undifferentiated mesenchymal tissue. When osteoblasts differentiate from the mass, these cells temporarily lose their glycogen. Just prior to mineralization, both osteoblasts and osteocytes contain abundant glycogen and maintain this content throughout the stages of development and calcification.⁴

Calcium and phosphorus combinations enter into calcification of both cartilage and bone. This material is ingested and absorbed through the intestinal wall into the blood stream. Thence it passes out through the endothelial walls of the capillaries to bathe

the tissues such as cartilage and bone. From here it diffuses through the intercellular substance to the cells. If the cells produce the proper enzymes to favor release of phosphorus from bound forms as phosphorus and sugar compounds or phosphoric esters, these chemicals deposit as calcium phosphorus complexes in the intercellular structure.

The gel of cartilage and intercellular substance of bone may well have a physical or a chemical affinity, or both, which precipitates calcium salts.

Bengt Sylén believes that loss of chondroitin sulfuric acid by cartilage allows for the calcifying action of alkaline phosphatase. If acid is present, it inhibits alkaline phosphatase action.¹¹

MODELING OF BONE

This process has been known and identified since the beautiful madder experiments of John Hunter. However, recently many experimental data related in particular to bone reabsorption and its underlying mechanisms have been collected. Here again, work has been directed toward how this comes about rather than toward simply observing a progressive series of events.

Bones grow but maintain relative proportion through modeling. In this way the general relationship of the medullary cavity to the entire bone diameter remains fairly constant in infant or adult (Fig. 12). Furthermore, by this process the original shape of each specific bone is maintained throughout the individual's development and life.

The process of modeling means the shaping of both the exterior and the interior of bone. This is done by a constant interplay of bone absorption and bone formation (Fig. 12). Derangement in modeling processes may be observed in osteopetrosis (marble bones) and in Paget's disease (osteitis deformans). Physiologic remodeling of bone in excessive degree occurs in the callus of healing fractures.

From the beginning of bone formation, modeling occurs. It will shape cartilage—

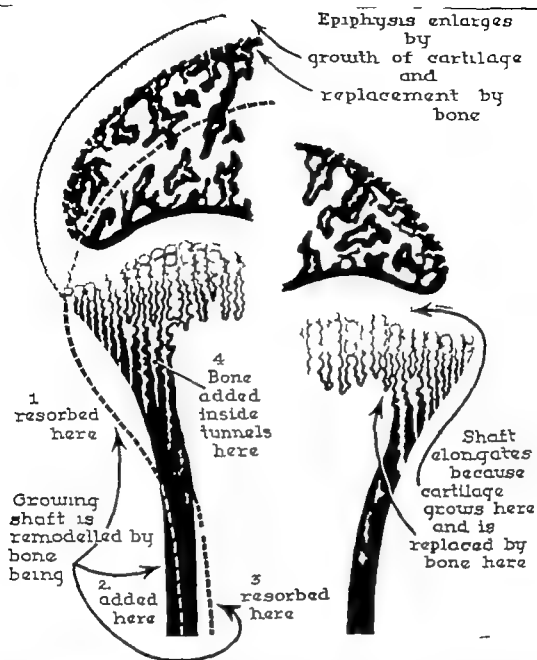


FIG. 12 Modeling at the end of a long bone. The interplay of bone deposition and reabsorption is shown. (From Ham A. W. Some histophysiological problems peculiar to calcified tissues *J Bone & Joint Surg* 34A 711 1952)

i.e. the early cartilage mold of endochondral bone formation (Fig. 7). It will shape young bone when the perichondral splint forms and the cartilage matrix is invaded by capillaries at the junction of the cartilage plate and the shaft (Figs. 8, 9). This cartilage matrix

becomes calcified and replaced by bone. It will also model bone itself (Fig. 12). It must be confessed that the basic "organizer mechanism" is not understood. It is this factor for example which makes a fetal femur a miniature of the adult femur.

REABSORPTION OF BONE

Reabsorption of bone occurs after physical injury to bone and after x ray irradiation. It occurs under areas of localized pressure. It takes place around metastases to bone and in certain diseases such as osteomalacia and Paget's disease.

Reabsorption of bone is observed in newly formed callus in the healing of fractures and in infections of bone and after large amounts of parathyroid hormone derived either from injection or from glandular hyperplasia or adenomata.

Reabsorption of bone occurs normally in the remodeling which takes place during growth. It occurs in the accessory trabecula located in the marrow of egg laying birds in connection with calcification of the egg shell.⁸ On a very high calcium and phosphorus intake growing rats develop greater spongiosa formation than do rats on a normal calcium and phosphorus intake. This indicates that the process of bone reabsorption does not keep pace with the excess bone formation engendered by the excessively high phosphorus-calcium intake.⁹ Reabsorption of bone will occur also under grafts of parathyroid tissue seemingly without cellular reaction or effect.⁸

Heller¹² applying Hotchkiss stain techniques applicable only in frozen dried bone attempted to correlate the reabsorption and the formation of bone with the content of glycogen and glycoproteins. The deep color indicated that these substances were less polymerized in bone being rapidly laid down and reabsorbed than in completely formed bone where the color was pale and indicated a higher degree of polymerization of the glycogen and the glycoproteins.

Bloom⁶ observed marked change in the ground substance of bone around the bone cells after the administration of large amounts of parathyroid hormone. Liberation of osteocytes made possible by dissolution of the bone matrix could be followed easily. Heller¹² used the silver method for staining bone salt. By this method when it

was observed that there was intense blackening of matrix in the zone of reabsorption it was interpreted as a greater solubility of bone salt and therefore a greater reactivity with the silver nitrate.

CRYSTAL CHEMISTRY OF BONE

Basic bone salt generally has been considered to be a hydroxyapatite. This is a complex salt composed of tricalcium phosphate and calcium hydroxide in a proportion of 3:1. The formula is $[\text{Ca}_3(\text{PO}_4)_2]_2 \cdot \text{Ca}(\text{OH})_2$. This would infer a calcium phosphorus ratio of 2:14. This formula dates from the work of Hoppe in 1862 who compared the composition of the mineral fraction of bone with apatite salts and found the atomic ratios to be similar. DeJong in 1926 through examination of bone by x ray diffraction concluded that bone salt was an apatite.

Three points of view on the crystalline structure of bone none fully substantiated are currently advanced. Dallemagne¹³ says it is a tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$. The $\text{Ca}(\text{OH})_2$ he considers to be adsorbed but not a part of the crystalline lattice. In addition calcium magnesium sodium and potassium carbonates are also considered to be adsorbed and not a part of the lattice. McConnell¹⁴ considers that bone is a carbonate apatite and thus the carbon dioxide as carbonate groups occurs within the crystalline lattice of dentin, dental enamel and bone. He feels that all these are similar to the mineral francolite. Hendricks⁷ has indicated that bone has the characteristics of a hydroxyapatite yet since the calcium-to-phosphorus ratio is 1:94 it has the composition of a tricalcium phosphate.

It is reasonable therefore to consider this effect as due to a hydroxyapatite with excess phosphate upon the surface. The exact nature of this excess phosphate is not yet identified clearly. Hendricks indicates that bone forms in a system of $\text{Mg}(\text{OH})^+$ and $(\text{HPO}_4)^{-}$ in the presence of carbonate. As the bone crystal grows in the form of a

hydroxyapatite it adsorbs carbonate magnesium and sodium ions. These materials then completely seal the crystal surface thereby stopping its growth. Such a mechanism limits the size of the crystal. New surfaces may form and cover the old one as occurs in enamel. New surfaces may occur as independent crystals which is the case in bone.

Obviously, there is still much disagreement about the precise crystal chemistry of the inorganic minerals yet enough has been demonstrated to cause much provocative thought.

It does appear that there is a basic crystal lattice and that this lattice has minerals upon its surface. If this be true then the old idea of halisteresis may not be altogether wrong. Bone absorption may occur in two separate or concomitant processes. One may be by halisteresis through an absorption of surface minerals such as magnesium or phosphate the other by a breakdown of the crystal (calcium and phosphate combination).

It is suggested that the inorganic lattice first precipitates into osteoid tissue and later evolves into a more complex structure by progressive adsorption of the other ions. This is not solely a process of simple precipitation. This complex of ions may induce a fundamental change in the matrix, a denaturation of the protein ground substance or other factors may produce such a denaturation of the protein ground substance thereby making combination with the inorganic material possible.

One of the enigmas of bone chemistry is the fact that though the product of calcium and phosphorus ion concentration exceeds the solubility constant for $\text{Ca}_3(\text{PO}_4)_2$, there is normally only selective deposition in certain areas.

CONCLUSIONS

An attempt has been made to indicate what is definitely known about the structure

and the development of cartilage and bone. Histology and gross anatomy have been reviewed in areas where information is fairly conclusive such as the conventional studies on hyaline cartilage, elastic cartilage and fibrocartilage and on the familiar subdivision of cortical cancellous and medullary bone.

Considerable interesting provocative but unfortunately as yet unfinished investigative information on the matrix of bone and cartilage has been presented. The tentative structures of the protein fiber and the polysaccharide interfibrillary substance have been indicated as far as they are known.

Similar material on the as yet unsolved crystal chemistry of the calcified bone matrix also has been discussed. An understanding of these data, known and speculative, is important for both the clinical and the research worker.

The basic problem of how and why bone and also cartilage form and grow cannot be answered definitely at this writing. Certain problems all suitable for further research work and ultimately of tremendous practical importance to clinical medicine, are suggested. Since the osteocyte cannot divide bone in itself cannot grow. Obviously bone does grow in both diameter and length.

The primitive anlage of bone of either endochondral, membranous or mixed type is formed from cellular structure which has the capacity to divide. Once mature bone has formed its keystone is the "osteone" of LeCroix.¹³ This consists of an inner osteocyte whose processes extend outward in canaliculi. The canaliculi are located in the matrix or the connective tissue. The "osteones" are closely adjacent to Volkmann's canals and the Haversian system which carry the nutritive materials to these end areas.

The osteocyte in the mature "osteone" does not have the capacity to divide. When it dies it must be replaced as indeed the entire "osteone" must be replaced by differentiating primitive connective tissue cells.

For when the osteocyte dies its matrix dissolves away

We find therefore that reticulum cells from the endosteum and the marrow areas and fibroblasts from the periosteum or the parosteal area may differentiate into osteoblasts, osteoclasts and osteocytes. The life of the osteoclast is shortest. The osteoclast can destroy the bone matrix formed by many osteoblasts in a fraction of the time required to produce it.

Much speculation about substances that may induce bone formation has gone on. LaCroix highlights the thought that there is an active principle that produces bone formation. He has called it "osteogenin." It is a provocative thought and one is led to consider the possibility of some such active

stimulant agent when the mode of bone formation and destruction is noted.

Why does connective tissue differentiate to form bone? Why does an osteocyte apparently die and have to be replaced? Does some material form when an "osteone" as LaCroix terms it dies and is absorbed? Are other materials necessary to activate any inductor enzyme or hormone that is released? Ribose nucleic acid appears to contribute to such an effect. Alkaline phosphatase also appears to be important in this phase of bone production.

It is in this field that more basic work must be done. Perhaps the contents of a syringe containing a proper bone stimulant may prove to be more osteogenetic than a mass of fresh bone.

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Inorganic (Mineral) Metabolism of Bone

INTRODUCTION

The physiology and the pathology of the skeletal system, in which nothing is so constant as change, cannot be understood without a thorough knowledge of the constituent minerals. From 4 to 5 per cent of the body weight is mineral matter. It exists in all fluids and tissues but especially in bone, teeth and cartilage. It is present principally as the various compounds of phosphorus, calcium, magnesium, sodium, potassium, iron and chlorine.

About 99 per cent of the calcium, 80 per cent of the phosphorus and the magnesium and smaller amounts of the sulfur, the sodium and the chlorine are present in bone where the organic matrix is impregnated with minerals. Large quantities of phosphorus, potassium and sulfur are associated with nitrogen in the formation and the functioning of muscular, glandular, renal and epithelial tissues. The large proportion of minerals in the intracellular and the extracellular fluid compartments are in effect mineral reserves. In a person weighing 148 pounds the proportion of the chemical elements is as follows:

	Percentage
Oxygen	92.4
Carbon	31.6
Hydrogen	14.6
Nitrogen	4.6
Calcium	2.8
Phosphorus	1.4
Potassium	0.34
Sulfur	0.24
Chlorine	0.12
Sodium	0.12
Magnesium	0.04
Fluorine	0.02
Iron	0.02

Cobalt, copper, iodine, manganese, silicon and zinc are found as traces. From the authors' viewpoint the more important electropositive minerals or cations include calcium, magnesium, sodium and potassium; the more important electronegative minerals or anions are phosphorus, sulfur and chlorine. When there is an excess of positive minerals in the food intake the diet is designated as alkaline-ash. Conversely, a preponderance of negative minerals in the food intake is called an acid-ash diet.

Retention of both positive and negative mineral elements is essential to growth. Under normal conditions the body requires a slight excess of positive minerals. Positive mineral retention is indicative of a trend toward skeletal growth or mineral storage in the skeletal system. Loss of positive mineral indicates breakdown or deficient formation of bone.

PHOSPHORUS

Introduction. Phosphorus, a nonmetallic element, does not occur free in nature. It is found in the form of complex minerals such as chlorapatite, fluorapatite, vivianite, evianite and phosphate rock or phosphorite.

The pure element can be isolated chemically in two forms, white and red. The poisonous white or yellow phosphorus is oxidized readily in air, is ignited easily and glows in the dark. It has the taste and the odor of garlic. Red phosphorus is an allotropic form of the element, produced by heating yellow phosphorus in the absence of air. It is nonvolatile, insoluble, nonabsorbable and therefore nontoxic.

Yellow phosphorus, which is insoluble in

water is soluble in fats and bile and therefore can be absorbed from the intestinal tract as well as from the subcutaneous tissues. This is true particularly if it is administered in a finely divided form. This element is toxic in relatively small amounts when injected in pure form. Manifestations of phosphorus poisoning in people who made yellow phosphorus matches were observed frequently—osteomyelitis and periostitis of the mandible ensued.¹ Some cases also were reported in which changes in the whole bony skeleton were observed. Because of its toxicity this type of match is no longer manufactured.

Forms Found in the Body The importance of phosphorus is indicated by its widespread presence in the organism and its many physiologic uses. In the blood serum it occurs as a completely ionized inorganic phosphate. It is found in organic form in the blood cells.

About 80 per cent of phosphorus is found in the skeleton where it is combined with calcium as complex apatite or triple phosphate salts. With the use of radioactive phosphorus (P^{32}) Hevesy and others analyzed the deposition of phosphate in bone.² The work of these and of other investigators³ led to the conclusion that bone contains two varieties of phosphate—a *labile fraction* in continuous exchange with the phosphate ions of the blood and a *stable fraction* which remains fixed in the skeleton. The circulating phosphate appears to enter the skeleton either by exchange a process of little significance in bone growth or by precipitation in definite areas with the formation of new bone.

Phosphorus Requirements. Sherman⁴ found the minimum phosphorus requirement for the normal adult to be about 0.88 Gm per day. The suggested intake is about 1.25 Gm per day in adults. For growing children the average requirement is about 1.3 Gm per day. A somewhat larger amount is needed by women during the periods of pregnancy and lactation and following lactation to make up for the losses which have

occurred from the body, particularly from the bones.

Food Sources of Phosphorus The phosphorus content of the diet is maintained at a proper level most readily through the liberal use of milk. A quart of milk contains 0.88 Gm of phosphorus. Other excellent sources of dietary phosphorus are meat (average content of phosphorus 0.15 mg per 100 Gm), eggs (0.18 mg), cheese (0.68 mg), nuts (0.40 mg) and whole cereals such as whole wheat (0.42 mg). White flour and polished rice are much lower in phosphorus content.

Phosphorus occurs in food as phosphatides or phospholipids, phosphorus-containing nucleoproteins and inorganic phosphorus. Research indicates that animals apparently can maintain phosphorus equilibrium on either inorganic or organic phosphorus alone,⁵ but that probably a combination of these elements is preferable.⁶

Absorption of Phosphorus Absorption of phosphorus in the small intestine occurs in the form of soluble inorganic phosphate. Complex ingested organic nucleoproteins must be broken down enzymatically by the pancreatic juices and the succus entericus. The component phosphoric acid is hydrolyzed presumably by the phosphatase found in abundance in the intestinal wall. It is transported across the cell membrane in combination with calcium.

Absorption of phosphorus is dependent upon vitamin D. This effect is presumably primary upon the calcium with only a secondary effect upon the phosphorus,⁷ since the calcium and the phosphorus usually are combined in a single molecule. Similarly, other factors in phosphorus absorption are related to calcium. A large excess of dietary calcium in proportion to phosphorus will interfere with absorption of both elements. This occurs because the excess calcium in the intestinal tract will combine with most of the phosphorus and discharge in the stool. Furthermore, some additional surplus calcium will cross the intestinal wall in the form of carbonates, chlorides or hydroxides.

If the excess calcium intake above phosphorus is maintained the bone will become depleted of phosphorus because the unrequired calcium in the blood stream will withdraw phosphorus from the bone structure.

Conversely if inadequate calcium intake occurs, there is an excess of phosphorus. This too will result in excess output of both in the stool for the transport of both calcium and phosphorus across the intestinal wall is dependent upon a reasonably balanced intake of both elements and is aided further by the effect of an acid medium (from the gastric juice) to increase solubility and vitamin D to increase absorption.

Transport of Phosphorus. Transport of phosphorus is a function of the blood. Blood-serum phosphorus is completely ionized inorganic phosphate. In infants, serum inorganic phosphorus is 5 to 6 mg per 100 cc. This gradually diminishes with age until the adult value of 3 to 4 mg per 100 cc is reached.

The amount of phosphorus in the blood cells is about five times that in the serum. Total phosphorus values in whole blood therefore, are higher than the serum inorganic phosphorus and represent the additional cellular organic phosphate esters, lipid phosphorus and phosphorus nucleoproteins.

Metabolism. In addition to the role in the ossification of bones phosphorus participates in many other phases of metabolism which can only be indicated rather than discussed fully.

The breakdown of carbohydrates to alcohol, lactic acid and sometimes eventually to carbon dioxide and ester depends on certain important phosphorus-containing compounds and enzymes. It has been shown that:

1. Hexosephosphate esters are intermediate substances in a series of important step-reactions in carbohydrate metabolism.

2. Three co-enzyme systems of great importance contain phosphorus. These are the adenylic acid system which is involved in phosphorylation reactions, the pyridine-

nucleotide system which plays a part in oxidation-reduction reactions and thiamine pyrophosphate which is important in the decarboxylation of pyruvic acid.

3. In the phosphorylation reactions, in intermediate compounds are formed which upon hydrolysis yield large amounts of energy.

Phospholipids are formed in significant amounts in many body tissues. Their concentration is greater in organs of young individuals. It has been suggested that this phospholipid content is an index of the extent and the variety of the organ's physiologic functions. Phospholipids form colloidal suspensions in water and can thus cross cell membranes.

Monoamino-monophospholipids of importance in the human⁸ are (1) lecithin which is composed of glycerol and two fatty acids, the third acid being replaced by the phosphoric acid-nitrogenous base known as choline and (2) cephalin, where the nitrogenous base is amino-ethanol. Lecithins and cephalins vary among themselves in the fatty acids they contain.

Sphingomyelin is a diamino-monophospholipid in which one portion of the tri-glyceride has been replaced by the base sphingosine and the other by the same phosphoric acid-choline complex as in lecithin.

The cerebrosides do not contain phosphorus but consist of sphingosine combined with galactose and a specific fatty acid. In phrenosin this is phrenosinic acid $C_{24}H_{44}O_4$ and in kersin lignoceric acid $C_{27}H_{54}O_4$.

This information may throw some light on certain disease states.^{9, 10} For instance Gaucher's disease is a rare familial reticulo-endothelial deposition of the cerebroside kersin. Its osseous manifestations are secondary to the kersin laid down in the reticulum cells of the bone marrow.

Niemann-Pick's disease affects principally infants, especially those of Jewish extraction and consists of generalized reticuloendothelial deposition of the diamino-monophospholipid sphingomyelin. It is nonhereditary and runs an acute rapidly

fatal course. At one time cerebromacular degeneration or the amaurotic family idiocy of Tay Sachs was considered to be identical but excess amounts of sphingomyelin have not been found consistently in the central nervous system.¹¹

Some individuals may consider that Hand Schüller Christian disease is related to the above conditions and that this is also a lipid storage disease. It appears however that this condition as well as eosinophilic granuloma and Letterer Siwe disease, are granulomatous processes. In the Hand Schüller-Christian syndrome it is felt that various amounts of cholesterol have been accumulated secondarily.

Excretion of Phosphorus. Phosphorus is excreted in the urine principally as monosodium (acid) and disodium (alkaline) phosphates NaH_2PO_4 and Na_2HPO_4 respectively. A lesser amount is combined with potassium to form similar salts of this metal. The remaining 25 per cent of the inorganic urinary phosphorus is found as ammonium, calcium and magnesium salts. The inorganic phosphates comprise 90 per cent of the total phosphorus excreted in the urine. The remaining 10 per cent are found as organic phosphates: namely glycerophosphates, hexosephosphates and nucleotides.

The relative proportions of monobasic (acid) and dibasic (alkaline) phosphates help determine the pH of the urine. Relative increase of the monobasic phosphate conserves not only fixed base largely sodium but also potassium magnesium and calcium.

Urinary excretion of inorganic phosphorus is affected by several factors which influence various components of the excretory mechanism. Increased phosphorus intake as in a high-protein diet, increased protein catabolism, as in severe starvation or vigorous muscular activity and gout—all are accompanied by an increase in total urinary phosphorus output.

Phosphorus is filtered through the glomeruli in direct proportion to the serum level. Low-phosphorus rickets and osteo-

malacia result in decreased urinary phosphorus output. Renal glomerular disease such as congenital cystic kidneys, obstructive lesions and chronic glomerulonephritis is accompanied by failure of filtration and consequent rise in serum inorganic phosphorus (hyperphosphatemia). Phosphorus is filtered by the glomeruli and reabsorbed through the tubules (Fig. 16). The latter is clearly controlled by the action of parathyroid hormone (Fig. 16 Section C).¹²

Parathyroid hormone administration inhibits phosphorus tubular reabsorption and hence results in hyperphosphaturia. Parathyroid hormone in adequate quantities may totally inhibit tubular reabsorption (Fig. 16 Section C III and IV). However other factors may also affect tubular reabsorption of phosphorus but to lesser degree. A lowered alkali reserve in the blood will decrease the reabsorption of phosphorus in the tubules. The pituitary or hypothalamic region of the brain may play some role. In pregnancy urinary phosphorus is also reduced possibly on the basis of increased tubular reabsorption.

CALCIUM

Introduction. Calcium, one of the alkaline earth metals, is a silvery white metal found in nature principally as calcium carbonate (limestone, marble, chalk and Iceland spar). It occurs also as dolomite, fluorite, gypsum, wollastonite and phosphorite. The pure metal has no commercial value but its compounds are used widely.

Forms Found in the Body. Calcium is a constituent of all animal fluids and tissues. Its presence is indispensable to life. It constitutes about 2 per cent of the weight of the adult body, about 99 per cent of the body calcium is found in the skeleton.¹ It occurs predominantly in combination with phosphate, carbonates and hydroxides.

Unlike phosphorus it is not found in available protective amounts in most foods. Only milk which contains 1.2 Gm. of calcium per quart and milk products such as

cheese (900 mg of calcium per 100 Gm) are completely satisfactory dietary sources of calcium. Breads contain phytic acid, which impedes calcium and magnesium absorption and therefore, makes the 30 to 40 mg of calcium for 100 Gm of foodstuff largely unavailable. Certain green vegetables such as spinach, while high in calcium content, are not adequate sources because of the oxalic acid which forms insoluble compounds with calcium so that it is not utilized by the body.²

Calcium Requirements. Sherman gives the daily calcium requirement for a 70 kg adult as 0.65 Gm. The National Research Council figure is 0.80 Gm. For children of from 3 to 14 years the minimum dietary calcium should be 1.0 Gm daily. In pregnancy during which 20 to 30 Gm of the mineral are deposited in the fetus, at least this much calcium must be included in the diet most conveniently on the basis of a daily quart of milk. Over 60 per cent of the fetal skeletal calcium is laid down in the last trimester.³

Lactation requires a similar amount of dietary calcium. The breast fed infant is maintained by about 45 mg of calcium per kilogram the formula fed infant by about 150 mg per kilogram. This discrepancy results from the fact that 50 to 70 per cent of the calcium in human milk is retained as compared with about 30 to 35 per cent of that in cow's milk.²

Absorption of Calcium. Calcium is present in both organic and inorganic forms in food. Conversion to the inorganic form probably must occur in the upper alimentary tract before absorption.

Absorption is favored by the acid reaction of the upper small intestine and this is where most of the calcium salts cross the intestinal wall. The most important factor maintaining the proper small intestine hydrogen ion concentration for calcium-salt solubility is the acid secretion of the stomach. Interference with calcium absorption has been noted with achlorhydria. Sugars especially lactose and amino acids also

provide a proper acid medium for calcium solubility and adsorption.¹

Vitamin D causes increased calcium retention in infants with rickets with a normal decreased fecal excretion and a negligible increase in the urine. In normal adults large doses of vitamin D initially decrease the proportion of calcium in the urine. After a few days this action is reversed and the main effect is to increase significantly the proportion of calcium excreted in the urine without altering the total excretion.⁴

This above work of Bauer, et al. appeared to show that vitamin D had little or no effect in physiologic doses on the ultimate absorption or retention of calcium in non-deficient individuals.

Recent use of very large doses of steroid vitamin D preparations in the possible therapy of arthritis resulted in metastatic soft tissue calcifications most often renal but also occurring elsewhere. It is felt currently that here there was overretention of calcium secondary to the ergosterol. Other possible explanations are an exaggeration of the normal vitamin D calcifying action or else a soft tissue injury secondary to toxic levels of the steroid with secondary dystrophic calcification in the affected areas.

Work conducted at Peiping Union Medical School⁵ and by Agnes Scott⁶ in India indicated that true vitamin-D lack with resultant osteomalacia is seen in adults who are not exposed to sunlight for social reasons and who ingest insufficient ergosterol. The defect lies in the lack of absorption of calcium from the intestinal tract. Oral calcium is ineffective and is merely lost in the feces. Intravenous calcium even without vitamin-D administration or exposure to sunlight reverses the negative calcium balance and produces calcification of skeletal osteoid.

It is thus clear that vitamin D is necessary in both adults and children for the absorption of calcium across the intestinal wall. This calcium in turn increases absorption as a result of the formation of insoluble calcium soaps. Similarly sprue

steatorrhea and celiac states interfere with calcium absorption because of the increased fatty acid content of the feces as well as the reduction of vitamin D absorption in these entities

As noted under phosphorus the calcium phosphorus ratio of ingested food is more important than the absolute amounts provided minimal requirements are exceeded.⁷ Excess phosphorus in the diet will interfere with calcium absorption by forming relatively insoluble calcium phosphate. Conversely on low phosphorus intake not only does excess calcium interfere with adequate phosphorus utilization but also other cations which form insoluble phosphates can cause experimental low phosphorus rickets. These include beryllium strontium magnesium iron lead and thallium.⁸

Calcium in the Blood; Transport and Metabolism. Calcium exists in the blood in two forms nondiffusible and diffusible.⁹ In life calcium is practically all found in the plasma since the red blood corpuscles contain only trace amounts. Following clotting it is found in the serum and it is this serum calcium which is determined by the usual laboratory methods.

The usual adult value for serum calcium in adults is 9.10-11.5 mg. per 100 cc. In infancy it is slightly higher.

It is important to note that the serum contains about three times as much calcium as can be held in inorganic solution at the same pH. This results from the presence of both nondiffusible and diffusible calcium in the serum. The breakdown of calcium fractions in the serum is approximately as follows:¹⁰

	Mg. per 100 cc.
Nondiffusible	40-50
Diffusible	50-65
Ionized	4.75-6.75
Un-ionized	0.25

Diffusibility of calcium is determined by compensation dialysis ultrafiltration technic

and vividiffusion. For all practical purposes nondiffusible calcium is protein bound although minimal amounts also are found as colloidal complexes of calcium phosphate. These colloidal complexes usually are present in the serum only in minute quantities or not at all. They are formed when either calcium or phosphorus is given in sizable quantities or following parathyroid hormone or vitamin D administration. This fraction disappears rapidly from the blood stream may be taken up by the reticulo-endothelial cells and may not be available for bone-salt formation.

Correlation of the various functions of the plasma-protein pool in respect to affinity for calcium has not been worked out. It is known that practically protein free body fluid like cerebrospinal fluid contains almost only diffusible calcium in a concentration approximately the same as that of the plasma. However if one believes that the cerebrospinal fluid is secreted rather than filtered by the choroid plexus even this point is not valid from a quantitative aspect.

Of the diffusible calcium almost all is in ionized form. Direct measurement of the ionic fraction was carried out by McLean and Hastings in 1934¹¹ using a biologic method. By measuring the amplitude of contraction of perfused frog heart ventricular muscle they were able to compare unknown solutions with calcium-chloride standards. It was determined that in protein-containing human fluids (i.e., serum ascitic fluid or edema fluid) the ionization of calcium followed the law of mass action. The specific equation for calcium is shown at the bottom of this page.

Thus if the calcium and the total protein concentrations in human serum or other protein-containing fluid are known the ionic calcium concentration can be calculated. It should be noted that the calculations must be carried out in millimols per liter not in

$$\frac{(\text{Ca}^{++})(\text{Protein}^{-})}{(\text{Ca-Proteinate})} = K = 10^{-3.21 \pm 0.07}$$

milligrams per 100 cc. The nomogram of McLean and Hastings summarizes the calculations (Fig 13) It can be seen from this that the serum protein is the principal determinant of ionized calcium Ca^{++}

HYPERCALCEMIA. Prolonged elevation of serum-calcium levels above 10.5 or 11.0 mg per 100 cc. is almost pathognomonic of hyperparathyroidism Experimental administration of parathyroid hormone will produce a similar biochemical sequence. This will include hypercalcemia, hypophosphatemia hypercalcuria and hyperphosphaturia.¹⁵ This sequence and the theories of parathyroid hormone *modus operandi* are discussed in the section on the parathyroid gland

HYPOCALCEMIA. Neuromuscular irritability has been known for many years to be controlled by ionic concentration and pH¹² The classic relationship is as follows⁹

Irritability $\propto \frac{(Na^+) + (K^+)}{(Ca^{++}) + (Mg^{++}) + (H^+)}$

All clinical forms of tetany in man result from relation to diminished total or ionized serum calcium or to alkalosis¹⁴

Hypocalcemic tetany is not merely dependent on the total serum calcium it also reflects the degree of ionization This in turn depends on the serum protein. Furthermore the rate of fall is important. For example postparathyroidectomy tetany following the surgical procedure may occur

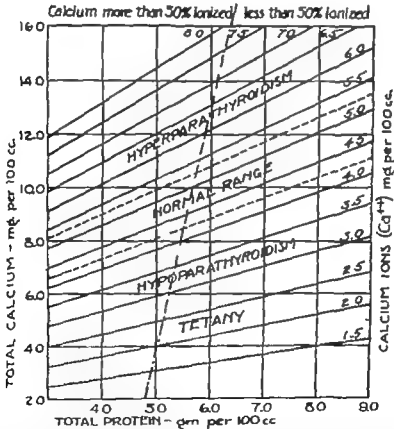


FIG. 13 Nomogram for the determination of ionized calcium concentration from total protein and total calcium values of serum. Note that at any given total calcium concentration ionized calcium varies inversely with the total protein concentration (From McLean, F. C. and Hastings, A. B. *Clinical Nutrition and significance of calcium ion concentrations in the blood* Am J M Sc. 189 606)

at serum concentrations of total and diffusible calcium which are ordinarily considered as above the tetanic level.

In general serum-calcium levels in man fall to or below 7 mg per 100 cc. in hypocalcemic tetanic states; the ionized calcium is less than 4.0 mg per 100 cc. by the McLean-Hastings nomogram.¹² Neuromuscular hyperexcitability as evidenced by jerking movements or occasionally by generalized convulsions is the outstanding finding.

Latent tetany is noted when the serum ionized calcium remains just above the critical level. Three well known methods are used to detect this condition. They are: (1) *Chvostek's sign*—tapping over the facial nerve in front of the ear results in twitching of the facial muscles; (2) *Trousseau's sign*—obstruction of the brachial artery above the elbow by a blood-pressure cuff or digital pressure results in carpal spasm with the wrist and the metacarpophalangeal joints held in flexion; the interphalangeal joints held in extension and the thumb adducted into the palm; and (3) *Erb's sign*—increased excitability of muscles to galvanic current.

Clinically hypocalcemic tetany is associated with decreased calcium intake or absorption, elevated serum phosphorus and increased urinary excretion of calcium, possibly because of a lowered renal threshold.^{8, 13}

The nutritional causes of hypocalcemia include vitamin D deficiency in children (rickets) and adults (osteomalacia) and gastro-intestinal disturbances like the celiac syndrome, idiopathic steatorrhea, sprue and oxalate poisoning.

Elevation of serum phosphorus may depress the serum calcium below the actual tetanic level. Combined renal tubular and glomerular disease is the commonest cause of hyperphosphatemic tetany. Here the glomerular filtration of phosphorus is lowered and adequate tubular excretion cannot occur. There may be an associated inability of the tubules to conserve calcium.

Citrate injections will cause tetany.¹⁴ The total serum calcium is normal but citrate forms a complex with ionized serum calcium.

Parathyroidectomy will result in tetany because of elevated serum phosphorus and lowered serum calcium. The mechanism involved may be primarily on the basis of phosphorus control, calcium control or a combination of both. At any rate symptoms abate with the use of high calcium intake oral or intravenous parathyroid extract, AT 10 and vitamin D.

Alkaline tetany occurs in relation to the various shifts of the bicarbonate-carbon dioxide ratios of the serum. Elevation of the serum bicarbonate may be relative or actual.

Relative or respiratory alkalosis occurs with hyperpnea where carbon dioxide lost through the alveoli makes for a temporary relative excess of plasma bicarbonate and consequent tetany.

Actual or metabolic alkalosis may follow excess sodium-bicarbonate ingestion or loss of gastric chloride ions in persistent vomiting as in pyloric obstruction. Adequate fixed base is available to balance the actual increase of plasma bicarbonate which ensues. Tetany may result from the metabolic alkalosis.

Excretion¹⁵ of Calcium. About 65 to 75 per cent of normal calcium loss occurs in the feces. This constitutes about 0.4 to 0.8 Gm. daily for the average adult on an ordinary diet. This largely represents calcium excreted continuously through the wall of the large bowel although a small proportion is made up of the unabsorbed ingested calcium as noted above.

About 150 to 250 mg. of calcium are lost daily in the urine. This mechanism is under the control of the parathyroid gland probably in response to the serum-calcium level.

Only ionized serum calcium passes the glomerular barrier, since the protein-bound fraction which is equal to about 55 per cent of the total serum calcium is too large a molecule to be filtered through. Most of this glomerular filtrate ionized calcium is reabsorbed in the renal tubes.

Parathyroid hormone acts to increase the amount of tubular reabsorption of calcium and thus decrease urinary calcium excretion (Fig 16). Since the level of parathyroid hormone activity may be considered to be in inverse ratio to the serum-calcium level the kidney thus acts to maintain homeostasis in respect to this level¹⁹ (Fig 16 Section D).

In secondary hyperparathyroidism such as is seen in renal disease so-called renal rickets the elevated serum phosphorus results in a reciprocal serum-calcium fall. Parathyroid hyperplasia attempts to conserve calcium further by restricting renal excretion through the aforementioned mechanism of increasing tubular reabsorption¹⁹ (Fig 16 Section D III).

In primary hyperparathyroidism increased serum calcium results from the osteoclastic effects of the hormone. The renal glomerular filtrate level of calcium is high because of the elevated serum level. The homeostatic property of the hormone on the tubules is not enough to conserve calcium from being lost in excess amounts in the urine in advanced cases. It is possible to conceive of an early case where increased tubular calcium reabsorption might balance the excess glomerular filtrate level for a short time.

Tubular disease of the Fanconi and the Albright Butler types is accompanied by a defect of the calcium reabsorption mechanism in the renal tubules¹⁹. This may be aggravated by an additional defect in ammonia production further intensifying the loss of fixed base including calcium. Idiopathic hypercalciuria is characterized by an isolated failure to reabsorb calcium.²¹

The estimation of urinary calcium by the Sulkowitch test is a useful indication of the level of urinary calcium excretion and secondarily of blood serum-calcium levels.

ESTIMATION OF URINARY CALCIUM

Principle: Precipitation of calcium as calcium oxalate

Instructions to patient: A prescribed low

calcium diet is followed for 3 days. On the third day beginning in the morning, a 24-hour specimen of urine is collected. A 4-ounce sample of this specimen is brought to the office.

The low-calcium diet, formulated by Albright and Reifenstein* and reproduced with permission is as follows:

Breakfast

Orange juice—1 small glass
Cooked Farina or rice— $\frac{1}{2}$ cup after cooking
4 Uneda biscuits
Oleomargarine
3 strips of crisp bacon
Coffee or tea
Salt and sugar

Noon

Lean meat—medium sized serving
Potato—1 medium sized
White corn— $\frac{1}{2}$ cup
4 Uneda biscuits
Oleomargarine
Applesauce— $\frac{1}{2}$ cup—or 1 medium-sized apple
Tea, salt and pepper, sugar

Night

Chicken—1 medium serving
Macaroni— $\frac{1}{2}$ cup (cooked)
Canned tomato— $\frac{1}{2}$ cup
4 Uneda biscuits
Oleomargarine
Banana—1 medium-sized
Tea or coffee
Salt, pepper, sugar

Note: Use oleomargarine and sugar generously to keep up weight. Absolutely no butter, milk, cheese, or cream. This diet contains approximately 0.137 Gm of calcium. Caution must be exercised to avoid cereals and oleomargarine which have been fortified with additional calcium.

Reagents: Sulkowitch solution

Oxalic acid	2.5 Gm.
Ammonium oxalate	2.5 Gm
Glacial acetic acid	5.0 cc.
Distilled water q.s.	150.0 cc.

* From *The Parathyroid Glands and Metabolic Bone Disease* p 75 Baltimore, Williams and Wilkins, 1948

Procedure:

- 1 A portion of the urine if turbid is centrifuged and supernatant fluid used for the test
- 2 3 cc. of reagent is added slowly to 3 cc. of urine and mixed
- 3 After 2 minutes the degree of turbidity of the precipitate is read in a graded scale of 0 to 4 plus (flocculent precipitate)

Interpretation: The renal threshold of serum calcium is 7.5 mg per 100 cc. of serum. A zero test indicates hypocalcemia a 3 to 4 plus test suggests hypercalcemia (more than 10.5 mg per 100 cc.) as in hyperparathyroidism

MAGNESIUM

Magnesium is a solid element which is found abundantly in nature. The most common form is dolomite which is a double carbonate of magnesium and calcium. It is also found as magnesite, as carnallite and as various silicates. It is present in many natural spring waters as epsom salt $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$. In pure state it is a silvery white metal, light in weight, with considerable structural strength. It tarnishes in air as the result of the formation of a magnesium-carbonate film which makes it self protecting.

Davy in 1808 first obtained magnesium in metallic form by electrolysis of a mixture of magnesium and mercuric oxides. This element is one of the most common in the crust of the earth (about 2.1 per cent).

Form in the Body: Magnesium is found in the animal in comparatively large amounts. The total for a 70-kg. adult is 21 Gm. It occurs chiefly in the bones and the muscles—in fact it is in greater concentration in the muscles than is calcium. Approximately 71 per cent of magnesium contained in the body is found in the skeleton.

Magnesium Requirements: Very little is known of the bodily requirement for magnesium. Wendt¹ suggests as a standard 0.01 Gm. per kilogram of body weight. This amounts to 0.70 Gm. per day for the average

adult. Tibbitts and Aub² showed a small positive balance on a magnesium intake of 0.22 Gm. per day. An intake between these two figures therefore would be a reasonable one.

Food Sources of Magnesium: The main natural source of magnesium is chlorophyll; hence it is found mostly in green vegetables and in milk, since the cow feeds primarily upon green plant life.

Absorption and Excretion of Magnesium: In man, the absorption and the excretion of magnesium parallel those of calcium.³ Like calcium it is ingested in inorganic and organic forms. The latter represent chlorophyll combinations which are broken up in the stomach and the intestines. Magnesium is not absorbed well because of a dehydrating action.

On normal magnesium intakes 60 per cent of total excreted magnesium is fecal;⁴ the remainder is urinary. Higher intakes of magnesium increase the fecal-output proportion. Since little magnesium is retained and fairly generous amounts are excreted in both feces and urine, magnesium thus acts as both a cathartic and a diuretic. Acid ingestion shifts the proportion of excretion from the feces to the urine.

Actual retention of magnesium is small. It is greater in infants than in adults for the healthy adult approximates equilibrium, whereas the growing child is in positive mineral balance.

When magnesium intake is deficient, the skeleton will still absorb it and bone will show increased calcium and phosphorus deposition.^{5, 6} It is possible that this occurs because magnesium is absorbed upon the bone crystals, thereby limiting its growth⁶ and encouraging the formation of additional crystals.

High-calcium intake intensifies magnesium-deficiency effects and raises magnesium requirement.⁶ High magnesium intake will produce rickets in growing animals particularly if phosphorus and calcium intake are low, presumably because of the formation of insoluble magnesium phosphates.

Blood Levels. Serum magnesium levels are 1 to 3 mg per 100 cc. The red blood cells contain much larger amounts of magnesium than does the serum. The level here may reach 5 to 8 mg per 100 cc.

Eighty per cent of the serum magnesium is ultrafiltrable, a higher proportion than that for diffusible calcium. The rest of the magnesium is largely in the form of a proteinate.

Serum-magnesium levels have not been observed to vary widely either in ordinary circumstances or in pathologic conditions. At times it has been observed to be low in rickets but it is not diagnostic of the condition.⁷

Levels of serum magnesium may vary as a result of the effect of other minerals, hormones and vitamins.

1. Injection of parathyroid hormone produces an elevation of serum magnesium which is again dissipated even before the induced calcium rise becomes maximal.⁸

2. Vitamin D may raise the serum magnesium slightly.

3. Injection of calcium salts causes the serum magnesium to rise, peak levels being reached in about 2 hours.

4. Injection of phosphate decreases magnesium levels before it affects calcium levels.

No matter how low the intake level is in the normal individual little effect upon the serum results. If, however, relatively small doses of soluble magnesium salts are given in the presence of severe kidney disease toxic effects and even death may result,⁹ because the serum magnesium level reaches a high concentration.

Mild sedative or hypnotic effects from magnesium may occur when the serum level reaches 5 mg per 100 cc. When 18 to 21 mg per 100 cc is reached profound coma and death result.¹⁰

Magnesium tetany associated with lowered blood serum levels occurs in cattle and is termed grass tetany.¹¹ It may also occur in calves reared on whole milk. The condition is due to very low magnesium intake.¹² Low magnesium tetany has not been ob-

McCollum showed that magnesium intake of 0.18 to 0.30 mg per 100 Gm of diet was too low to support life.¹³ Rats on such an intake developed convulsions and died. Electrical reactions¹⁴ demonstrated that this was a low magnesium tetany. In spite of low intake magnesium still deposited in bones but to one half the normal amount. Furthermore in the presence of deficient magnesium intake the bones become unusually heavy with calcium and phosphorus excess. If the calcium in the diet is raised the amount of magnesium for normal requirement is increased.

Metabolism. Magnesium is important in relation to neuromuscular irritability. When decreased in the blood tetany may result. When increased sedation and narcosis may occur. It is an antispasmodic and will reduce blood pressure.^{15, 16} It is a cathartic and a diuretic.

Magnesium appears to become adsorbed upon the surface crystal lattice in bone in the form of $MgOH_2$ and to contribute to sealing and preventing the continued growth of the crystal.¹⁷ It is related to factors of local calcification¹⁸ and appears to affect the deposition of calcium and phosphorus. It may inhibit local calcification but in a role as a synergist associated with strontium.

Studies¹⁹ on rachitic bone sections produced by low-phosphorus and high-calcium or high-strontium intakes revealed that magnesium enhanced the inhibitory effect of strontium on in vitro calcification. This occurred in strontium rickets but not in calcium rickets. A similar synergism for calcium rachitic sections occurred when cyanide or fluoride and magnesium were added to the calcifying bath. If magnesium was not present, cyanide or fluoride did not inhibit calcification.

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laxation of smooth muscle. This reaction did not occur when calcium or other cations were used.¹⁷

Many balance studies¹ demonstrate definite absorption of magnesium when it is given in increased amounts, particularly as the chloride or carbonate. This is observed through increase of urinary excretion of magnesium as well as by actual retention. When magnesium was administered in doses approximating 4 Gm daily, phosphorus retention was definitely reduced.

It appears furthermore that magnesium has a beneficial effect upon Paget's disease. This will be commented upon in detail under treatment of Paget's disease.

STRONTIUM

Strontium is an alkaline earth element. It is closely allied to magnesium, calcium and barium, as is evident on study of the periodic table. While its most common natural forms are the carbonate and the sulfate, other forms such as the lactate can be made.

This cation is not in abundant supply and plays little or no role in normal animal metabolism.

Since it is in the same group as calcium, similar compounds to those formed with calcium could be presumed. Biologically, also, these compounds might have similar or slightly varied effects. Work has been done with this element on heart muscle¹ and in bone. This latter field is of intense interest and is currently the subject of much investigation.

Alwens and Grassheim² used strontium as early as 1921 and determined no toxicity in the human even with the administration of a total of 360 Gm of strontium lactate. This was given in dosages of 3 Gm daily.

Strontium is not in sufficient concentration in foodstuffs so its normal intake for all practical purposes is nil. For an effect it must be ingested in the form of one of its salts. The best tolerated and seemingly the best absorbed is the lactate.³

On the basis of administration of strontium to experimental animals, Lehnerdt⁴

concluded that there was a twofold effect—one an increase in osteogenetic tissue and the other an induced sclerosis of this same tissue. In light of present knowledge we can interpret this as increasing osteoid production and increasing the mineralization of this osteoid. Subsequent work⁵ confirmed the observation of osteoid proliferation. It was hypothesized that the effect was related to a high phosphorus low-calcium rickets.

Shorr² reported studies upon strontium in cases of postmenopausal osteoporosis. In these studies he evaluated strontium in its relationship to the mineralization of osteoid.

In 1933 strontium carbonate was administered to children with rachitic deformities even though the active rickets had been controlled. It was used with the thought of removing phosphorus and producing an osteomalacic state. When achieved this could and did permit manual correction of deformities such as severe genu varum or valgum.⁶ The method was to eliminate vitamin D from the diet and to keep these patients upon a low-calcium and low-phosphorus diet. Strontium carbonate was then given. Spectroscopic studies of strontium levels in the blood reached as much as 50,000 times the usual level. When the bones were softened adequately and deformities corrected, a high-calcium, high-phosphorus vitamin D diet was given and healing ensued.

The trouble with this method is the inevitable production of generalized osteomalacia to allow correction in limited areas.

A strong specificity of strontium for phosphate may be presumed here. This would result in increased fecal strontium phosphate excretion as probably the primary mechanism in producing the osteomalacia.

Dramatic healing in "hunger osteopathy" was reported² with strontium administration in 1921. This was not controlled work and as can be inferred from the above must have been used with reasonable levels of phosphorus and calcium and vitamin D to have produced a healing effect. Else osteomalacia would have increased.

Blood Levels. Serum magnesium levels are 1 to 3 mg per 100 cc. The red blood cells contain much larger amounts of magnesium than does the serum. The level here may reach 5 to 8 mg per 100 cc.

Eighty per cent of the serum magnesium is ultrafiltrable a higher proportion than that for diffusible calcium. The rest of the magnesium is largely in the form of a proinate.

Serum magnesium levels have not been observed to vary widely either in ordinary circumstances or in pathologic conditions. At times it has been observed to be low in rickets but it is not diagnostic of the condition.⁷

Levels of serum magnesium may vary as a result of the effect of other minerals, hormones and vitamins.

1. Injection of parathyroid hormone produces an elevation of serum magnesium which is again dissipated even before the induced calcium rise becomes maximal.⁸

2. Vitamin D may raise the serum magnesium slightly.

3. Injection of calcium salts causes the serum magnesium to rise peak levels being reached in about 2 hours.

4. Injection of phosphate decreases magnesium levels before it affects calcium levels.

No matter how low the intake level is in the normal individual little effect upon the serum results. If however relatively small doses of soluble magnesium salts are given in the presence of severe kidney disease toxic effects and even death may result⁹ because the serum magnesium level reaches a high concentration.

Mild sedative or hypotonic effects from magnesium may occur when the serum level reaches 5 mg per 100 cc. When 18 to 21 mg per 100 cc is reached profound coma and death result.¹⁰

Magnesium tetany associated with lowered blood-serum levels occurs in cattle and is termed grass tetany.¹¹ It may also occur in calves reared on whole milk. The condition is due to very low magnesium intake.¹² Low-magnesium tetany has not been observed in human subjects.

McCullum showed that magnesium intake of 0.18 to 0.30 mg. per 100 Gm. of diet was too low to support life.¹³ Rats on such an intake developed convulsions and died. Electrical reactions¹⁴ demonstrated that this was a low-magnesium tetany. In spite of low intake magnesium still deposited in bones but to one half the normal amount. Furthermore, in the presence of deficient magnesium intake, the bones become unusually heavy with calcium and phosphorus excess. If the calcium in the diet is raised the amount of magnesium for normal requirement is increased.

Metabolism. Magnesium is important in relation to neuromuscular irritability. When decreased in the blood tetany may result. When increased, sedation and narcosis may occur. It is an antispasmodic and will reduce blood pressure.^{15, 16} It is a cathartic and a diuretic.

Magnesium appears to become adsorbed upon the surface crystal lattice in bone in the form of $MgOH_2$ and to contribute to sealing and preventing the continued growth of the crystal.¹⁷ It is related to factors of local calcification¹⁸ and appears to affect the deposition of calcium and phosphorus. It may inhibit local calcification but in a role as a synergist associated with strontium.

Studies¹⁹ on rachitic bone sections produced by low phosphorus and high-calcium or high-strontium intakes revealed that magnesium enhanced the inhibitory effect of strontium on *in vitro* calcification. This occurred in strontium rickets but not in calcium rickets. A similar synergism for calcium-rachitic sections occurred when cyanide or fluoride and magnesium were added to the calcifying bath. If magnesium was not present, cyanide or fluoride did not inhibit calcification.

It appears therefore that magnesium may be a local calcification inhibitor and that strontium also may have a similar effect but in a different part of the local calcification mechanism.

Magnesium salts in normal serum ionic concentration have been used in a modified Dale apparatus and have demonstrated re-

laxation of smooth muscle. This reaction did not occur when calcium or other cations were used.¹¹

Many balance studies¹ demonstrate definite absorption of magnesium when it is given in increased amounts, particularly as the chloride or carbonate. This is observed through increase of urinary excretion of magnesium as well as by actual retention. When magnesium was administered in doses approximating 4 Gm daily, phosphorus retention was definitely reduced.

It appears furthermore that magnesium has a beneficial effect upon Paget's disease. This will be commented upon in detail under treatment of Paget's disease.

STRONTIUM

Strontium is an alkaline earth element. It is closely allied to magnesium, calcium and barium as is evident on study of the periodic table. While its most common natural forms are the carbonate and the sulfate, other forms such as the lactate can be made.

This cation is not in abundant supply and plays little or no role in normal animal metabolism.

Since it is in the same group as calcium similar compounds to those formed with calcium could be presumed. Biologically, also, these compounds might have similar or slightly varied effects. Work has been done with this element on heart muscle² and in bone. This latter field is of intense interest and is currently the subject of much investigation.

Alwens and Grassheim³ used strontium as early as 1921 and determined no toxicity in the human even with the administration of a total of 360 Gm. of strontium lactate. This was given in dosages of 3 Gm. daily.

Strontium is not in sufficient concentration in foodstuffs so its normal intake for all practical purposes is nil. For an effect it must be ingested in the form of one of its salts. The best tolerated and seemingly the best absorbed is the lactate.²

On the basis of administration of strontium to experimental animals, Lehnerdt⁴

concluded that there was a twofold effect—one an increase in osteogenetic tissue and the other an induced sclerosis of this same tissue. In light of present knowledge we can interpret this as increasing osteoid production and increasing the mineralization of this osteoid. Subsequent work⁵ confirmed the observation of osteoid proliferation. It was hypothesized that the effect was related to a high phosphorus low-calcium rickets.

Shorr⁵ reported studies upon strontium in cases of postmenopausal osteoporosis. In these studies he evaluated strontium in its relationship to the mineralization of osteoid.

In 1933 strontium carbonate was administered to children with rachitic deformities even though the active rickets had been controlled. It was used with the thought of removing phosphorus and producing an osteomalacic state. When achieved this could and did permit manual correction of deformities such as severe genu varum or valgum.⁶ The method was to eliminate vitamin D from the diet and to keep these patients upon a low-calcium and low-phosphorus diet. Strontium carbonate was then given. Spectroscopic studies of strontium levels in the blood reached as much as 50,000 times the usual level. When the bones were softened adequately and deformities corrected a high-calcium, high-phosphorus vitamin D diet was given and healing ensued.

The trouble with this method is the inevitable production of generalized osteomalacia to allow correction in limited areas.

A strong specificity of strontium for phosphate may be presumed here. This would result in increased fecal strontium-phosphate excretion as probably the primary mechanism in producing the osteomalacia.

Dramatic healing in "hunger osteopathy" was reported⁷ with strontium administration in 1921. This was not controlled work and as can be inferred from the above must have been used with reasonable levels of phosphorus and calcium and vitamin D to have produced a healing effect. Else osteomalacia would have increased.

Strontium in the form of the lactate was reported to be absorbed best even to greater degree than calcium when administered in equivalent amounts.² Furthermore it appeared that strontium lactate caused an increase in calcium storage. When strontium was discontinued the increased calcium retention continued for as long as 10 days.

Further long term balance studies⁷ in a patient suffering from postmenopausal osteoporosis seemed to indicate that the sum of strontium and calcium retained with a fixed phosphorus intake was greater than the maximum retention of calcium when it was given alone.

Androgens estrogens and vitamin D increased the storage of both strontium and calcium. Furthermore it appeared that the strontium was retained in the form of strontium phosphate.

Studies upon radioactive strontium⁸ indicated that the material was distributed similarly to radioactive calcium but to a lesser extent.

In vitro calcification studies⁹ with rabbit skeletal sections showed deposition of strontium in the epiphyseal areas when Sr was substituted for Ca.

It appears that strontium is clearly utilized as a strontium phosphate. Therefore when phosphorus intake is low it must compete with calcium and protein for phosphorus in order to be deposited in bone. Testosterone because of protein anabolism may prevent strontium absorption because phosphorus is tied up in nitrogen storage if phosphorus intake is low. However if phosphorus intake is great enough to satisfy both protein and calcium requirements then it will be available for strontium absorption and deposition. Under these circumstances strontium will then be able to maintain its seeming ability to enhance calcium absorption.

It is reasonable on the above hypothesis to consider that strontium may well act as an additive mineralizing agent, although it is not proved that it enters the bone lattice in the same way that calcium does.

However it may be presumed to be active and absorbed with calcium and nitrogen if the phosphorus intake is sufficiently high. So not alone is an adequate calcium-phosphorus-protein intake of value but also increased phosphorus in the form of strontium-phosphate salts may be highly desirable.

SODIUM

Sodium is a member of the alkali metal group. It is very active chemically with only one electron in the outer ring. It does not occur free in nature but is found principally as the chloride and the nitrate and as cryolite.

It is a soft silvery metal which tarnishes when exposed to air and decomposes water at room temperature. It decomposes water to form sodium hydroxide and releases hydrogen.

Forms Found in the Body. The usual compounds of sodium are water soluble. In the animal organism sodium is the largest fraction of the total fixed base. It is almost completely ionized in the body even in the sodium proteinate form. It is associated most commonly in osmotic equilibrium with the chloride and the bicarbonate.

The sodium content in the adult is 60 to 65 Gm. It occurs principally in the extracellular fluid—that is the plasma and the interstitial compartments.

It is not found in the red blood cells. Most of the sodium unaccounted for in interstitial fluids is in the skeletal tissues with cartilage in particular having a particularly high content.¹

Sodium Requirements. The normal intake for an adult human is 4 Gm. of sodium or 10 Gm. of sodium chloride per day. The maximum intake without accumulating edema fluid is 35 to 40 Gm. of sodium chloride per day.

The blood level is 160 mg. per 100 cc. whole blood, 340 mg. per 100 cc. for plasma. These can be converted to milliequivalents per liter by multiplying by 10 and dividing

by the molecular weight of 23. The figure would therefore be 147.8 milliequivalents per liter of plasma.

Sodium is absorbed through the gastrointestinal tract. Furthermore there is a tremendous turnover of sodium in the intestinal tract since much sodium is contained in the secretory juices and has to be reabsorbed.

Excretion of Sodium. The kidney is the principal organ for the excretion of water sodium potassium chloride and sulfate. Under most circumstances sodium and chloride occur in the urine in approximately equal amounts. Abnormal losses of either sodium or chlorides must be balanced by the kidney. For example if chloride is lost by vomiting then bicarbonate substitutes for it in the urine.

When no sodium or chloride is ingested or in fasting states practically none of either is found in the urine. Similarly if sodium or chloride is lost by excessive sweating or by way of the bowel urinary excretion is diminished. Usually the feces contain only small amounts of sodium.

Metabolism. Desoxycorticosterone is particularly active as an agent to enhance sodium storage. The mechanism involves diminution of renal excretion of sodium and substitution of potassium for sodium in the urine. Cortisone and hydrocortisone have similar effects. Indeed in using these hormones care to avoid edema from excess sodium retention must be taken. Further more potassium loss must be anticipated and provided for with increased potassium intake.

These hormones act by increasing the tubular reabsorption of glomerular filtrate sodium and decreasing the tubular reabsorption of potassium. It is of interest that a similar mechanism although much smaller in degree occurs in the sweat.²

Excess of adrenal hormones affecting sodium and potassium results in sodium retention and loss of potassium. This causes lowered serum potassium and depletion of intracellular potassium. The increased so-

dium causes an elevation of serum sodium and edema as well as hypertension since the water volume is excessive. Furthermore sodium in these circumstances will migrate into cells and displace potassium. Sodium reacts to water intake. So if water is withheld, plasma sodium concentration increases. Water has already been drawn from the extracellular compartment for renal excretion. The increased sodium in the plasma then draws out intracellular fluids with potassium. The potassium and the water are then excreted through the kidney.

In Addison's disease or similar states sodium conservation cannot occur. Extracellular water and sodium are excreted rapidly by the kidneys. The plasma-sodium concentration falls. Water migrates intracellularly and the serum potassium level will increase. As a result the untreated Addisonian is susceptible to deprivation of sodium and water.

Location and Metabolism of Sodium in the Bone. Studies utilizing tracer substances cannot work in bone as in other tissues. The usual division is to consider an organism composed of intracellular, interstitial and plasma fluid compartments. Bone is composed largely of extracellular solids and these are not freely permeable to all traces.³ There is considerable sodium and water in bone¹ including marrow as well as matrix solids. Approximately 30 per cent of body sodium and 8 per cent of body water is located in bone. Consistent figures of 220 milliequivalents per kilogram of dry fat free bone have been established.¹

Tissue sodium is freely exchangeable with serum sodium. The maximal exchange is established at about 50 per cent.² These conclusions were established by studies of sodium exchange in dogs on a rice salt-poor milk and sugar diet. Sodium²² with a 3 year half life was used rather than sodium²⁴ with a 15-hour half life. In this way studies for an entire month with relatively constant tracer concentration were possible.

Sodium is on the surface of the apatite crystal lattice⁴ and there is a larger amount

of exchangeable sodium than calcium.² It has also been considered that sodium and calcium are the same molecular size although they differ in charge. For this reason they may be interchangeable to fit upon the surface of the bone crystal.³

POTASSIUM

Potassium is a soft, silvery white alkali metal. It tarnishes on exposure to air and becomes brittle at low temperatures. It is one of the most active metals and reacts vigorously with oxygen, the halogens and water. It stands just below sodium on the periodic table.

Forms Found in the Body. Its compounds are water soluble. Its role in man and the primates is primarily that of an intercellular substance and as such it occurs in rather large concentration especially in the muscles. For example, fresh muscle contains 365 mg. of potassium per 100 Gm.

In the human body as a whole there are 150 Gm. of potassium. This compares with 63 Gm. of sodium and 1,160 Gm. of calcium.¹ The skeleton contains 6.4 Gm. of potassium and the muscle mass 109 Gm. In relation to the total potassium in the body, therefore, the amount found in bone is quantitatively insignificant.

Potassium Requirements. Like sodium, potassium is essential to life. The normal daily intake for an adult human is 2 to 3 Gm. This is obtained easily in any diet adequate for other needs. Ingestion of amounts above 20 Gm. is apt to cause edema.¹

The blood level is 5 milliequivalents per liter in the plasma. This represents 19.5 mg. per 100 cc. of plasma.

The potassium content of the red cell is 170 milliequivalents per liter, which is approximately 34 times that of the plasma. Intact red cells have walls that prevent egress of potassium and entrance of sodium. A similar phenomenon occurs in intact muscle cells in regard to the surrounding interstitial fluid.² This is important in that

blood potassium levels may appear at normal levels or rise when tissue breakdown is occurring.² Here the total amount of body potassium by radioactive studies is low even when hyperkalemia may be present.²

Potassium depletion occurs in gastrointestinal disorders, including faulty absorption and increased loss as a result of diarrhea and vomiting. Potassium depletion also occurs in malnutrition states. It develops in chronic congestive heart failure where diuretics are used or when ion-exchange resins are administered. Marked loss of potassium through the kidney with sodium retention occurs as a result of excess dosages of cortisone, hydrocortisone or adrenal corticotropic hormone. This is something to be particularly careful about because of stress states and the common usage of the above hormones.

When a patient is on intravenous feedings over a period of time it is important to maintain potassium levels. Blood-plasma studies may be deceiving as a result of tissue breakdown as discussed above, so when intravenous feeding is carried out potassium also must be used up to 2 Gm. daily with a check of blood plasma and if necessary, urinary excretion. In this way adequate amounts will be given and the bad effects of hyperkalemia will not occur.

The principal regulation of potassium is in the kidney. Normally small elevations of serum-potassium level are reflected by marked increases in urinary excretion.³

When the serum-potassium level falls urinary excretion is reduced. The reduction takes place slowly so that serious loss of potassium may occur. The reason this occurs is that patients have concurrent sodium retaining stimulating mechanisms. These stimuli are from the pituitary or the adrenal and may cause ion exchange of potassium for sodium in the distal tubular segments of the kidney.⁴

When potassium depletion is chronic the kidney mechanisms come into play and the kidneys may excrete less than 1 milliequivalent of potassium per day.⁵

Associated with potassium loss from tissue catabolism is nitrogen loss from tumors infection diabetes starvation and post stress states such as operations and trauma For every gram of nitrogen that is lost 2, milliequivalents of potassium are also lost⁴

Hypokalemia is manifested by a clinical picture of weakness of the extremities sometimes progressing to actual flaccid muscle paralysis This may involve even the muscles of respiration

Delirium and actual tetany secondary to hypokalemic alkalosis may occur the explanation for which is postulated by Darrow⁷

Hypokalemic alkalosis represents a relative increase of plasma bicarbonate which follows the shift of sodium into the intracellular compartment This occurs as replacement of the potassium loss This may be observed indirectly by a fall in blood chlorides—a hypochloremic alkalosis This however can occur in either sodium or potassium depletion So when tetany occurs and potassium depletion is suspected it is well to check the plasma bicarbonate the sodium and the potassium, as well as the EKG

Elevation of bicarbonate and normal sodium with low potassium will indicate an acute hypokalemic alkalosis The EKG pattern is typical for hypokalemia

Hyperkalemia is observed when the normal kidney excretory mechanism is impaired It will occur on excess potassium release as in trauma, in renal disease in ad renal insufficiency as in Addison's disease and in diabetic coma when protein is broken down.

The symptoms of hyperkalemia are mental confusion weakness ascending paralysis numbness and tingling of the extremities thickness of speech, difficulty in walking loss of tendon reflexes and bradycardia Death can occur from cardiac arrest.

EKG changes begin at the 5 milliequivalent per liter levels. They progress on to auricular standstill ventricular conduction

difficulties arrhythmias and finally cardiac arrest

From the point of view of the clinician hypokalemic and hyperkalemic states can be corrected If kidneys are working and proper amounts of potassium can be taken orally there is no problem of replacement or maintenance

Interesting research work on experimental animals has clearly delineated a relationship between potassium and nitrogen storage

Animals that were given potassium chloride in addition to the basal ration which was deficient in potassium grew at a greater rate than the controls which did not receive the inorganic supplement. Animals that received the potassium had better appetites and consequently consumed greater amounts of food Two groups of animals on equal caloric levels of energy intake showed less growth in the potassium-deficient animals Animals that received amino acid preparations orally plus additional amounts of potassium showed increased growth as compared with those animals on a similar diet, lacking potassium⁸

This fact appears significant in relation to patient care If amino acids and carbohydrates are administered parenterally potassium also should be given. This will favor proper utilization of the nitrogen. From the practical viewpoint maintenance of electrolytic requirements of potassium will be adequate for metabolic needs.

FLUORINE

Fluorine is a member of the halogen family Chemically it is the most active element known in regard to its reaction with metals and many nonmetals. It is a yellowish gas in its full state. It is found usually as fluorite and cryolite and as a fluorapatite. On ingestion either by mouth or by inhalation this element is absorbed by the body fluids Half of that absorbed will be taken up by the bone and the teeth and half excreted by the urine

Normal fluoride concentration in blood

body fluids muscle and other soft tissues is quite low. The amount is a few micrograms per 100 Gm. Increased ingestion of fluoride will not be reflected in the blood except for possibly very short intervals for the excess is excreted rapidly in the urine and deposited in the skeleton.

When the intake is approximately one part per million as is used in fluoridation of water apparently no particular ill-effect occurs. If the amount is greater as has been reported in one case (12 parts per million over a long period of time) severe toxicity and changes result. The toxic phase¹ may be referred to as crippling fluorosis.

A diagram illustrating the intake the absorption the effects and the excretion of fluorine has been published by Hodge² and is shown at the bottom of this page.

Deposition of fluoride in the skeleton will occur continuously as long as any fluoride is ingested whether large or minute in amount.^{3,4} No equilibrium stage is reached and bone stores of fluorine will not decrease as long as any level of intake is continued. The deposition of fluoride in bone would in fact, continue to increase.

The deposition of fluoride in bone occurs in two ways—one as an adsorption reaction upon the surface of the bone crystal.⁵ This occurs as a competitive exchange between fluoride and bicarbonate or hydroxyl ions. The second way is more complex and a

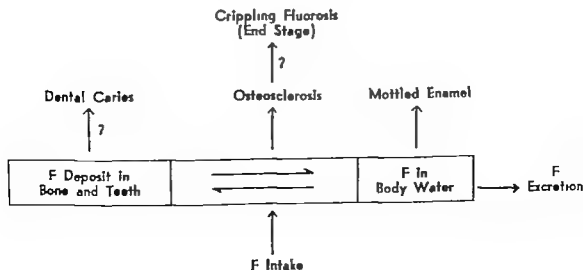
much slower process involving the incorporation of fluoride within the bone lattice.⁶ This may be described as recrystallization following osteoclasts.

Reabsorption of fluoride following cessation of ingestion of this material follows the same pattern as the deposition. A rapid urinary excretion occurs in the first month. This is the result of the loss of fluoride ions from the crystal surface and their replacement by hydroxyl and bicarbonate ions.⁷

Interpretation of this phenomenon makes it clear that consistent administration of fluoride in therapeutic doses is necessary to control caries. This assumes that fluoride adsorption protects against caries.

After the surface exchange occurs with resultant fluoride loss, following cessation of fluoride ingestion the slower loss of this material occurs by a process of recrystallization. This rate of loss in the human is of the order of a half time constant of 2 years—in other words 50 per cent will be lost in 2 years. In the next 2 years, 50 per cent of the remainder will be lost and so on ad infinitum.⁸

It appears that the skeleton, for fluorine as for other toxic metals acts as a detoxification mechanism. In that way it takes up half of the ingested fluorine the other half being excreted via the urine. If the amount of fluorine is small no ill effect occurs. If large in amount, an effect upon the amelo-



blasts resulting in mottled enamel occurs. Furthermore an effect upon osteoblasts must be presumed.

Johnson⁹ has summed up the abnormal matrix and skeletal findings in a single case resulting from large amounts of fluorine as follows:

The gross observation of the massive increase in weight and specific gravity which is expressed as osteosclerosis, the microscopic picture of abnormal Haversian patterns, failure of the Haversian systems to adhere together, laying down of a matrix material that you would call osteoid but does not have the normal/visual texture, being granular and lumpy. The reticulum collagen and polysaccharide components do not stain clearly as in normal bone. At times it looks as though the two proteins collagen and homogeneous polysaccharide protein are independently deposited without being welded into a single new substance, osteoid. Sometimes the involved trabeculae look parboiled in disorganization.

Roholm¹⁰ reported upon chronic fluoride intoxication among cryolite (aluminum fluoride) workers in Denmark and Greenland. X-ray findings were of widespread calcification of tendons, muscle sheaths, marked osteogenesis and extensive arthritic changes in the spine producing rigidity. The bones showed marked osteosclerosis resembling Paget's disease.

There is a question as to whether heteroionic migration of fluorine into the crystal lattice can occur in living bone.¹¹ There is not much doubt that fluoride may be adsorbed upon the crystal or even be present in the organic matrix. But it is not clear as to whether or not it may go actually into the crystal lattice.

BERYLLIUM

Beryllium is an alkaline earth metal. It was discovered by Vauquelin in 1797 in the mineral beryl and in emeralds. It was isolated as a metal independently by Wöhler and Bussy in 1828. In pure form it is either a gray powder or crystalline with the luster and the hardness of steel. Actually it is hard enough to scratch glass. It is soluble

in dilute acids and in alkali hydroxides. It is found as beryllium aluminum silicates.

The chemical reactions of beryllium resemble those of magnesium. Commercially it is used in light alloys. It has good electrical conductivity and tensile strength in the alloy form especially when combined with aluminum and copper. It is not a normal component in animal diet nor is it usual for most individuals to come in contact with it either by touch or by inhalation. In recent times, however, it has become an industrial hazard for it is used in fluorescent lights and also as a material entering into the formation of alloys, particularly with copper.

Toxicity. The toxic effects from beryllium are manifested in two ways: first, by local contact with the skin and the eyes in particular. Here it produces contact dermatitis, chemical conjunctivitis, corneal burns, non-healing ulceration at the site of injury and subcutaneous nodules. Second, by inhalation it may cause an acute pneumonitis which may be fatal. A chronic granulomatous disease may appear from 3 months to 6 years after exposure. This may follow exposure of short duration or of low concentration.

It appears that incredibly small concentrations, of its salts and even of the element itself, can produce these changes even to the point of causing death. It has long been known that beryllium can produce rickets, which state originally was considered to be due to phosphorus precipitation by beryllium in the intestinal tract.

Recent studies by Grier et al.,² and by Yü et al.,³ clearly demonstrate that this element has a blocking effect on bone and other tissue alkaline phosphatases.

Further in vitro studies have indicated that beryllium will retard the liberation of phosphorus from certain organic phosphoric esters by blocking the effect of alkaline phosphatase. In this way it interferes with calcification of tissue slices.³ However, it does not interfere with calcification in solutions containing inorganic phosphorus. It merely interferes with dephosphorylation of organic esters by alkaline phosphatase.

Beryllium acts upon the following organic esters: beta-glycerophosphate, phenyl phosphate, creatine phosphate, glucose-1 phosphate, and hexose diphosphate. Magnesium appears to overcome this beryllium inhibiting effect upon alkaline phosphatase.¹ The reason is that apparently beryllium competes with magnesium contained in the alkaline phosphatase molecule. This same observation applies also to manganese. It is of interest, also, that serum alkaline phosphatase is lowered in beryllium rickets.²⁻⁴

CADMIUM

Cadmium is a member of the zinc family of elements. These elements are bivalent and less active than the members of the alkali and the alkaline earth families. Cadmium was discovered by Stromeyer and Hermann, in 1818. It is a silver white blue tinged lustrous metal. Water and carbon dioxide react slowly upon the surface of the metal to form a basic carbonate which prevents further corrosion. It is found in small quantities associated with zinc ores, sulfides, oxides, and carbonates.

Cadmium is not normally ingested in foods. It has a high degree of toxicity. Ingestion of the metal or its compounds causes increased salivation, choking, vomiting, abdominal pain, diarrhea, and tenseness. Inhalation of cadmium dust or fumes causes throat dryness, cough, headache, vomiting, chest pain, extreme restlessness, and irritability, pneumonitis, and possibly bronchopneumonia.

In experimental work, it has a strong affinity for phosphorus and as a result may deplete phosphorus stores, thereby producing rachitic or osteomalacic states.

It is not clear, however, that cadmium has additional blocking effect upon local calcification as does beryllium.

COMPLEXING OR CHELATING AGENTS

These agents, of which Versene or Sequestrene are examples, have interesting effects upon the chemistry of the body.

The chemical name is ethylenediamine tetraacetic acid. (For simplicity in referring to this compound from here on it will be referred to as EDTA.) This compound forms a series of monosodium, disodium, trisodium, and tetrasodium or potassium salts which increase in water solubility with increasing degrees of neutralization.

From the medical point of view, the important function of this compound is its ability to form unusually stable complexes with the alkaline earths and the heavy metals.

The combination of this compound with cations is referred to as chelation. Once the complex is formed, the cation is bound securely and cannot be precipitated by common precipitating agents. It also loses its chemical ionic identity.

The equation that illustrates the chelating or complexing reaction with calcium as an example is

$$K = \frac{(\text{Ca EDTA})}{(\text{Ca}^{++})(\text{EDTA})}$$

K defines the ratio of calcium which occurs as the chelated complex to the calcium in the ionized state. This can be referred to as a stability constant. When K is large, the ionic concentration of the given metal will be low and the more stable will be the chelated complex.

EDTA will combine with practically any cation. The affinity of EDTA for a cation is in relation to the pH of the solution and the position of the metal in the periodic table.

In general, the more alkaline the solution, the greater the affinity; the higher the valence, the greater the affinity.

This compound, with its numerous salts and cation combinations, is a most interesting one from the point of view of industrial chemistry. There has been wider application in this field than in the field of medicine. However, as can be deduced from its general properties and characteristics listed above, certain applications in relation to the skeleton system are suggested as follows:

1. Metal detoxification application of

this chelating agent to the treatment of heavy metal poisoning. Work has been done with a calcium EDTA complex that seemingly allows for exchange of calcium for lead.¹ Application of this principle for other heavy metals may also prove reasonable.

2 Cation exchange in the blood and the tissue fluids. This is exemplified by the use of a magnesium EDTA complex to take up ionic calcium from the blood and to release ionic magnesium in exchange. This has been done in clinical studies on hypertension. Since the magnesium released produces marked vasodilatation and hypotension,² other substances might also be considered for ionic exchange including radioactive ones.

3 Since it will combine with ionic calcium and can even produce tetany if given rapidly enough and in sufficient quantity, it may have some value as an anticoagulant.⁴ It has been used with this in mind.

4 Since it may decalcify at a pH of 5 to 10.3, it should be of great value in preparing bone sections for alkaline phosphatase stains.

Calcium Versenate. The administration of the pre-formed calcium Versene complex has been shown to be without significant toxicity. In animals the minimum lethal dose for this compound is around 4,000 mg per kilogram by the intraperitoneal route as compared with ionic calcium salts which show the same toxicity at dose levels ranging around 40 mg per kilogram of calcium ions. It has been administered to humans clinically in dosages as high as 100 Gm. over a 20-day period without evidence of significant toxicity.

Magnesium Versenate. The magnesium salt of Versene exhibits very much the same toxicity as the chelating agent itself. This

has been shown to be the consequence of the exchange of the magnesium in this complex for calcium of the body and the physiologic conditions of pH and salt concentrations. The pharmacologic effects usually attributable to magnesium ion become evident to an enhanced degree under these conditions due to the concomitant removal of some of the calcium inhibition of magnesium ions. Predominant among these pharmacologic actions of magnesium ion are its marked vasodilatation with concomitant fall in blood pressure. This summation of action has been used clinically in hypertension.⁴ Chronic toxicity of this chelating agent does not appear to be evident.

Toxicity. The primary evidence of Versene toxicity is that of a hypocalcemic tetany. Rapid administration of this solution will produce death when the physiologically available calcium levels have dropped to a tetany level. In general, this will occur at a dose level of around 100 mg per kilogram either intravenously or intraperitoneally in most animals.³ If the solution is given more slowly so that the animal is able to replace the complex calcium from its calcium stores, death will not occur from the hypocalcemia.

In slow fashion therefore Versene has been given to humans in dosages up to 5 Gm. over a period ranging up to 24 hours. The effect on circulating calcium levels again appeared to be a function of the rapidity of the administration of the complexing agent.

It is possible that further study of these compounds may develop many more uses in medicine both from the experimental viewpoint in the study of trace metals in biologic systems and from the clinical viewpoint as in the treatment of urinary calculi,⁴ hypertensive states and for anticoagulant effect.

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Organic (Protein) Metabolism of Bone

Enormous amounts of work have been done upon the inorganic structure of bone. It was only more recently that bone became recognized as a living substance and that it is not simply a structure to accept inorganic material. Protein is a vital portion of all living tissue and bone is no exception. Therefore a review of general protein metabolism is desirable since optimum intake and absorption must favor skeletal development.

Occurrence. All living things plant and animal life contain proteins. The fundamental difference between animals and plants rests in the ability of plants to synthesize proteins. These are formed from the nitrogen and the sulfur of the soil and from the carbon, the oxygen and the hydrogen of the atmosphere. Animals must ingest proteins which then are broken down and rearranged to form the particular tissue proteins required.

Protein Requirements. The prevailing opinion is that 1 Gm. of protein is required for each kilogram of body weight in normal adults but that states of pregnancy, growth and lactation require greater amounts. Requirements must take into consideration the digestibility of proteins. Milk and eggs have a digestibility of 100 per cent. Meats run from 95 to 100 per cent. Legumes and potatoes have a value around 80 per cent. Wheat proteins have a value of 90 to 100 per cent.

Proteins contain component amino acids. Not all of these are considered to be essential to life and growth. The essential amino acids are 11 in number:

- | | |
|--------------|-----------------|
| 1 Arginine | 7 Norleucine |
| 2 Histidine | 8 Phenylalanine |
| 3 Isoleucine | 9 Threonine |
| 4 Leucine | 10 Tryptophane |
| 5 Lysine | 11 Valine |
| 6 Methionine | |

Nitrogen-balance studies equate the nitrogen of the diet against that of the urine and the feces. Since proteins contain about 16 per cent nitrogen, percentage nitrogen can be converted into percentage protein by multiplying by 6.25. The percentage of nitrogen retained in the body and not lost in the urine is the so-called biologic value of a protein.¹

Digestion and Absorption of Proteins. The gastric proteolytic enzyme pepsin hydrolyzes the protein molecule to proteoses and peptones. In the intestine the pancreatic enzyme trypsin liberates free amino acids from proteins. Also a carboxypolypeptidase from the pancreas with the enzymes from the intestinal secretions, acts upon the polypeptides to yield amino acids. Once the amino acids are formed they easily cross the intestinal wall. There is also evidence to indicate that polypeptides may be absorbed through the intestinal wall.² Proteins given in other form directly into the blood stream are apt to be toxic.

After absorption through the intestinal walls, amino acids go to the liver via the portal vein. Some continue via the systemic circulation and enter the tissues throughout the body. Within the liver some of the amino acids undergo deamination, resulting in the formation of ammonia and a carbohydrate residue. Further deamination goes

on in the kidney and probably in lesser degree in other tissues.

It has been known for a long time that protein will be broken down for energy if adequate carbohydrate is not available. For nitrogen economy 50 to 60 per cent of daily caloric intake must be supplied by carbohydrate.³

Protein ingestion stimulates the metabolism 30 per cent beyond its caloric value. This is referred to as the specific dynamic action of proteins. The figures for fats and carbohydrates are 4 and 6 per cent respectively.

Work on protein catabolism has been studied extensively by many workers utilizing many techniques. It appears that the greatest proportion of nitrogen released by amino-acid breakdown in man appears as urea.

Amino acids not required to supply tissue protein or not required for hormone elaboration are deaminated. The amino group is combined with carbon dioxide to form urea. The residual fatty acid residue is either oxidized into carbon dioxide and water or transmuted into glucose.

A separate metabolic cycle occurs in man in relation to the formation of uric acid. This represents the special end product of the catabolism of nucleoproteins containing a purine base in their nucleic acid.

The sequence of events in the metabolism of nucleoproteins to uric acid is as follows:

Nucleoproteins split into protein and nuclein by the action of pepsin.

Nuclein is hydrolyzed in protein and nucleic acid by the action of trypsin. Nucleic acid consists of 4 mononucleotides. Each of these is composed of the following: phosphoric acid, a pentose and a nitrogenous group (either a purine or a pyrimidine base).

In animal nucleic acid composed of the four mononucleotides 2 contain a purine base and 2 contain a pyrimidine base. The sugar is in the form of desoxyribose. The 2 purines are adenine and guanine; the 2 pyrimidines are thymine and cytosine.

Nucleic acid is hydrolyzed into the four nucleotides by enzymes termed nucleases. These are found in the intestinal wall and juices. The nucleotides are hydrolyzed by nucleotidases also originating in the intestinal wall. This results in the formation of phosphoric acid and the corresponding adenosine and guanosine nucleoside. Each nucleoside is broken down into a pentose and a purine by nucleosidases which occur in the intestinal wall and tissues. The purines in turn break down into the urinary end product of uric acid.

A summary of the above appears on the following page.⁴

In animals other than primates and the dalmatian coach hound 80 to 98 per cent of the uric acid is further oxidized by uricase to allantoin and CO₂. Allantoin is 250 times as soluble as uric acid and therefore is excreted easily.

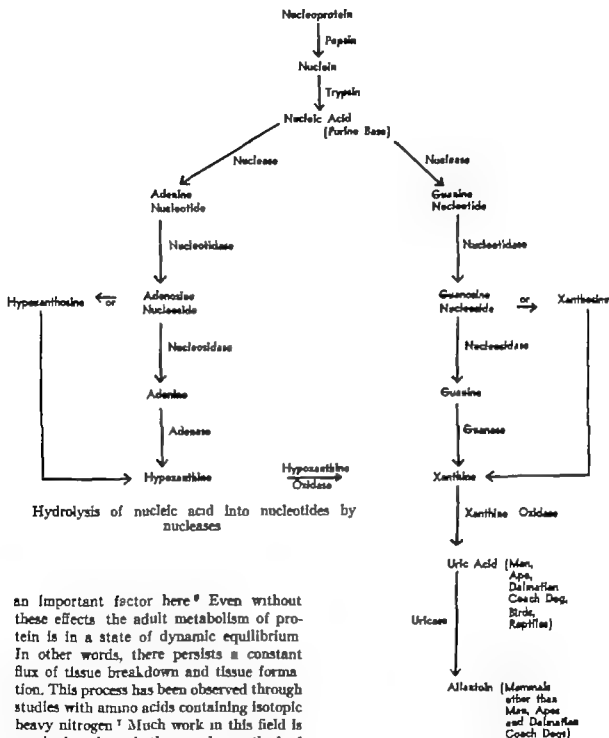
Purine synthesis occurs in mammals for they may be kept upon an almost purine free diet, yet excrete uric acid. Furthermore they apparently make nucleic acid for cell nuclei.

Histidine is the chief precursor of purines and a diet rich in this amino acid will increase uric acid excretion by over 30 per cent.⁴

Uric acid in man originates from two sources: exogenous or food and endogenous or body proteins. It appears that there is a relationship between gout and purine metabolism. There is a general but not a quantitative relationship between purine intake, gout and serum-uric acid levels.

Anabolism of Proteins. Comparatively little is known of the processes by which ingested amino acids are combined to form body proteins. Following amino-acid absorption via the portal system the blood level of these acids rises. Soon thereafter the level falls as these acids are taken up by the body tissues,⁵ especially the liver.

Build-up of protein from amino acids is particularly active during growth, pregnancy and lactation. The anterior pituitary, especially through the growth hormone, is



an important factor here.⁶ Even without these effects the adult metabolism of protein is in a state of dynamic equilibrium. In other words, there persists a constant flux of tissue breakdown and tissue formation. This process has been observed through studies with amino acids containing isotopic heavy nitrogen.⁷ Much work in this field is continuing through the simpler method of using radioactive isotopes.

In addition to amino-acid interchanges which are a part of dynamic equilibrium, increased protein catabolism occurs in stress states. Protein breakdown is increased by adrenal cortical hormones. Selye indicates that this endocrine gland becomes hyperactive in stress ("alarm reaction").⁸ Injury

and fever cause additional protein breakdown. Ulcers, burns and wounds excrete much protein through their transudates. Protein intake therefore in such conditions must be increased to achieve dynamic equilibrium.

Plasma Proteins. These are largely a prod

TABLE 1 PATHOLOGIC CONDITIONS ASSOCIATED WITH ALTERED SERUM PROTEIN CONCENTRATION*

HYPOPROTEINEMIA	HYPERTHYRINEMIA
Below 6.0 Gm per 100 cc.	Above 8.0 Gm per 100 cc
1 Malnutrition Dietary (a) Endemic and sporadic (b) Associated with chronic infection, pellagra, beriberi, etc. Poor absorption (a) Diarrhea (b) Intestinal fistulae, ileostomy	1 Dehydration Insufficient intake Fluid loss (a) Intestinal obstruction and fistulae (b) Diarrhea, especially of infants (c) Cholera (d) Diabetic acidosis (e) Vomiting (f) Burns (g) Heat exhaustion (h) Fulminant infections (i) Addison's disease
2 Kidney diseases Nephroses—all types Glomerular nephritis, chronic Amyloid kidney	2 Diseases involving bone marrow Multiple myeloma Malignant metastases to bone
3 Liver diseases Cirrhosis Cancer	3 Infections, chronic Syphilis, trypanosomiasis Subacute bacterial endocarditis Lymphogranuloma inguinale Leprosy kala-azar Boeck's sarcoid Malaria filariasis
4 Protein dilution Excess fluid administration Fever	4 Liver diseases Cirrhosis Cancer primary or metastatic
5 Protein loss Hemorrhage Weeping wounds Shock	
6 Heart failure Hyperthyroidism	
8 Chronic poisoning Benzene, war gases	
9 Toxemias of pregnancy	

Modified from Kaplan B M: The clinical significance of the serum proteins, South. Med. J. 35:236-237 1943

uct of the liver. They reflect two components: albumin and globulin. The precise mechanism of their formation is as yet unknown. These compounds may be subdivided by two different methods.

Plasma proteins are active in facilitating fluid, nutrient and protein exchange. The gamma-globulin component in addition is most important in the organism's defense against bacterial invasion.

However, it has been demonstrated that by plasmapheresis⁹ and low protein diets¹⁰ animals can be made hypoproteinemic.

Plasma proteins are found to be high in multiple myeloma, hypothyroidism, syphilis, other chronic infections (as tuberculosis) and hemoconcentration.¹¹

Gamma globulin is increased in acute

infections or suppurative processes. It is also increased in primary hepatocellular disease, kala-azar, leprosy, lymphogranuloma inguinale, granuloma inguinale, Still's disease and multiple myeloma. In the latter, Bence Jones protein is increased.

Plasma fibrinogen rises in acute infections, inflammatory conditions, trauma, hepatitis, lymphogranuloma inguinale, granuloma inguinale, nephrotic syndrome, multiple myeloma, sarcoidosis, menstruation, pregnancy and after radiotherapy.

Euglobulin is increased in malaria, kala-azar and sarcoidosis and oftentimes in multiple myeloma.

Hypoproteinemia may result from excessive loss, failure to ingest adequate amounts of proteins and failure to synthesize serum

proteins in the liver.¹¹ Hypoproteinemia in fers that albumin is diminished

Excess loss of protein occurs in nephritis the nephrotic syndrome fever hyperthyroidism burns and hemorrhage. In lipid nephrosis in addition to the albumin the gamma globulin is decreased and the beta globulin is increased

Failure to ingest adequate amounts of proteins occurs in malnutrition states diabetes mellitus improperly treated malignancy and excessive vomiting

In normal pregnancy plasma protein will decrease to 6 Gm per 100 cc. due to the transference of protein from mother to fetus

Decreased production of plasma proteins occurs in liver disease Fibrinogen is also markedly decreased in liver disease When serum albumin is less than 2.5 Gm per 100 cc., edema occurs

Plasma-protein fractions commonly have been determined in two ways The older technic is the Howe method—one of precipitation with ammonium or sodium sulfate of the various components of the plasma The results are as follows

1. Albumin 4 to 5 Gm per 100 cc. of human plasma
2. Globulin $\left\{ \begin{array}{l} \text{a Pseudoglobulin II } 0.3 \text{ to } 0.75 \\ \text{b Pseudoglobulin I } 0.9 \text{ to } 1.9 \\ \text{c Euglobulin } 0.2 \text{ to } 0.6 \end{array} \right.$
1.6 to 2.7
3. Fibrinogen 0.2 to 0.3

Normal albumin-globulin ratio is between 1.5 to 2

More recently fractionation of plasma proteins has been done by electrophoresis in the Tiselius apparatus By this method normal plasma yields the following

Albumin	4.6 to 5.4 Gm per 100 cc.
Globulin	
Alpha	
Beta	1.5 to 3.4
Gamma	
Fibrinogen	0.24 to 0.4

It appears from this work that in its native state serum globulin is apparently homomolecular The differentiation into pseudoglobulins and euglobulin by the older

salt-out technic is essentially an artificial one

Hormone Synthesis. Amino acids are the precursors of many body hormones Those considered are thyroglobulin thyroxine epinephrine pituitary hormones and insulin

Bone Protein. The organic portion of bone comprises over one half of its weight and two thirds of its volume Gils et al. reported in 1901 and 1902 upon fractionation studies of denatured bone protein Their method was first to demineralize bone by acid then to treat the organic residue with alkali This resulted in an alkaline extract aggregating 0.5 per cent of bone protein It was termed osseomucoid The remainder was soluble in water and was termed ossein Most of the ossein yielded gelatin when dissolved in hot water A small residue amounting to 0.3 per cent was termed osseoalbuminoid

As stated in the chapter on "Bone and Its Structure" actual investigative work on the precise nature of bone protein has been difficult because of the mineral content.

A demineralization technic denatures the protein mechanical methods tend to produce too much heat and result in changes in the nature of protein As a result, precise composition of bone protein is not understood clearly because no direct analytical chemical method could be used Many of the data have been derived by inference from work on softer tissues such as tendon skin and cartilage.

Robinson¹² used the electron microscope to study bone structure and thereby was able to determine certain facts in relation to the inorganic and the organic portions of bone. He observed that bone matrix consists of a protein collagen fibril with a mucopolysaccharide cement substance The collagen fibril of bone by electron microscopy appears similar to that of the collagen of connective tissue

It is well to recall that collagen has a specific amino-acid pattern¹³ There is a high glycine content approximating 25 per cent Two imino acids proline and hydroxy



FIG. 14. Decalcified human femur seen by electron microscopy. The major doublet bands of the collagen are spaced by 560 Å. The doublet bands are seen to continue across several fibers at right angles to the fiber direction. (From Robinson R. A. and Watson M. L. Collagen-crystal relationships in bone as seen in the electron microscope. *Anat. Rec.* 114:399, 1952.)

proline¹⁸ constitute approximately 30 per cent. Collagen alone is said to contain hydroxylysine¹⁸. However, collagen is said to contain no cystine or tryptophane. Only small amounts of tyrosine and methionine are present¹⁸. It must again be emphasized that these are all soft tissue studies. Another approach in bone-structure anal-

TABLE 2 CHEMICAL AND ANATOMIC COMPOSITION OF BONE*

COMPONENTS	PARTIAL DIVISIONS	YOUNG BONE			ESTABLISHED BONE			LONGER ESTABLISHED	
		WGT (Gm)	VOL. (CC.)	SPEC. GRAV	WGT (Gm)	VOL. (CC.)	SPEC. GRAV	WGT (Gm)	VOL. (CC.)
Inorganic	Ash weight of 100 Gm of fresh bone	43	14.3	3.0	51	17	3.0	55.0	18.5
Organic	Organic weight	23	14.2	1.62	27	16.6	1.62	28.4	17.7
	Organic weight + ash weight = dry-bone weight	66	28.5	2.32	78	33.6	2.32	83.4	36.0
Water		34	34	1.0	22	22	1.0	16.6	16.6
Total	100 Gm. of fresh, by dried bone without marrow	100	62.5	1.6	100	55.5	1.8	100	52.5
Constant	Ash weight = Dry weight =	$\frac{43}{66} = 65.2$			$\frac{51}{78} = 65.4$			$\frac{54.9}{83.4} = 65.8$	

From R. A. Robinson, M.D.

ysis x ray diffraction study confirms the existence of polypeptide chains in the form of collagen fibers.¹⁷

Collagen fibers are considered to be the crystalline part of the organic matrix.

The gelatin nitrogen of bone represents the protein in collagen fibers and constitutes 50 to 65 per cent of the total nitrogen.¹⁸

The nongelatin nitrogen represents the protein in the cement substance and cells.

The cement substance is formed by a number of hexose protein compounds. These include mucopolysaccharides and glycoproteins. The former is similar to chondroitin sulfate.

Calcification of matrix will not occur until collagen appears.²⁰ X-ray diffraction studies confirmed the appearance of the collagen before inorganic crystals appeared.²¹

By electron microscopy²² collagen fibers in bone form a three-dimensional network (Fig. 14). These films are about 800 angstrom units in thickness and show a double

banding which may be seen as links chain each 400 to 500 angstrom units. Each band may also link adjacent parallel collagen fibrils. The inorganic crystals fold and parallel these fibrils. At 640 angstrom-unit intervals these crystals rim the fibrils.

The interfibrillar spaces show no consistent parallelism to the fibers but do have a tendency to form a laminated structure.

A provocative thought about protein substances in bone is the possibility that the collagen fiber in itself may be an inducer to bone formation and calcification.

Flexible cancellous and immature bone contains more organic and less inorganic material than mature cortical bone. This is verified by electron microscopy.¹⁹ It shows a looser arrangement of the collagen fibers and the crystals. This may indicate the importance of collagen as a stimulus to bone formation.

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Enzymes as Related to Bone

ALKALINE PHOSPHATASE AND PHOSPHORYLASE

Alkaline phosphatase has been known for some time to be widely distributed in the body both in the tissues which ossify and in those which do not ossify. This has been termed the "bone enzyme." It appears in ossifying zones coincident with the beginning of this process and is more abundant in these zones than elsewhere. It is found in relatively high concentration in intestinal mucosa, liver, kidneys, ossifying cartilage, bone leukocytes and blood serum. Non-ossifying cartilage (e.g., trachea) shows no phosphatase activity. In generalized bone diseases (e.g., osteitis deformans, hyperparathyroidism, osteomalacia and active rickets) the alkaline phosphatase rises. This indicates that it must have an important role in the mineralization of the skeleton.

Robison evolved an interesting hypothesis in regard to role of this enzyme in relation to bone and cartilage¹ as follows: the osteoblasts and the hypertrophic cartilage cells secrete an active alkaline phosphatase which, by hydrolyzing the phosphoric esters of the blood, brings about a local increase in the concentration of phosphate ions. The solubility product of calcium phosphate thereby is exceeded and deposition of this salt occurs in the ossifying zone. The evidence in favor of this hypothesis was indicated to be as follows:

1. Phosphatase is present in growing bone and teeth in the greatest amount in those areas in which deposition of calcium phosphate is proceeding most rapidly.

2. It can be demonstrated in vitro that a growing bone split longitudinally will allow deposition of calcium phosphate from a solution of a soluble calcium-phosphoric

ester salt such as calcium hexosemonophosphate. Furthermore, deposition would occur mainly in the cells in the zone of provisional calcification.

3. Alkaline phosphatase appears in cartilage simultaneously with the appearance of centers of ossification.

4. There is no phosphatase in cartilage which is not ossifying—i.e., Meckel's cartilage of the mandible does not develop phosphatase whereas the membranous portion does.

5. In certain generalized diseases of bone the serum alkaline phosphatase is elevated. It is not elevated in other conditions except for obstructive liver disease.

This is a most ingenious and reasonable hypothesis for calcification and ossification. Unfortunately, it does not completely explain the mechanism of calcification. Certain objections may be raised to this hypothesis.

1. It does not take into consideration all possible actions of this enzyme. Considerable concentrations of alkaline phosphatase are observed in many tissues in which calcification or ossification does not occur.

2. Alkaline phosphatase acts to liberate inorganic phosphate from organic phosphate substrates. This action presumably occurs at the point of calcification or ossification. Yet practically 100 per cent of blood-serum phosphate is in the form of ionizable inorganic phosphorus. Moreover, the osteoid tissue that is to be calcified has no organic phosphorus for hydrolysis by this enzyme. It is true that there is organic phosphorus in the blood cells, but there is no evidence that phosphorus is liberated from this substrate.

So a second mechanism must be operative. This has been advanced by Harris² and

more recently by Gutman.³ The latter considers that a complex series of enzymatic reactions that are a part of phosphorylative glycogenolysis play a role in *in vitro* calcification of cartilage when phosphorus is provided as inorganic phosphate. The cycle goes to phosphopyruvate formation.

Alkaline phosphatase dephosphorylates phosphoric esters after phosphopyruvate formation.⁴

Studies on the role of alkaline phosphatase are aided by using beryllium salts which are a specific inhibitor of alkaline phosphatase in its role in *in vitro* calcification of cartilage.⁵

On studies on rat cartilage beryllium inhibited alkaline phosphatase activity.⁶ This blocked *in vitro* calcification of cartilage when phosphorus was supplied as beta glycerophosphate but had no inhibitory effect on cartilage calcification when inorganic phosphate was used.

The conclusion⁷ is that alkaline phosphatase is essential for *in vitro* calcification of cartilage when phosphorus is in the form of phosphoric esters. Alkaline phosphatase is not necessary when phosphorus is supplied as inorganic phosphate. This may be evident in endochondral calcification *in vivo*.

One can fit this nicely with the following observations. It has been observed that the glycogen present in the osteoblasts and the osteocytes is high until shortly before calcification or ossification occurs then the cells lose their glycogen. Shortly after the calcification and ossification effect occurs the glycogen is again observed in the cells.⁷ Furthermore it has been observed that phosphorylase which is found in growing cartilage and bone tissue appears to have an effect upon glycogen.^{2,4,8} It is quite reasonable to presume that its effect is a conversion of glycogen to glucose-1 phosphate and then to other phosphorus compounds. This material produced by phosphorylase could then be an organic substrate upon which phosphatase could act. Then the phosphorus would be liberated from such

a compound thereby allowing the deposition of a calcium phosphate complex as bone salt.

Further studies⁹ of alkaline phosphatase have been done by tissue-staining technique and by the incubation of freeze-dried material. Magnesium was substituted for calcium in the incubation medium. These techniques demonstrated that considerable concentrations of alkaline phosphatase were present in regions about to undergo calcification. Furthermore calcification processes in membranous bone were found to resemble that observed in the endochondral type. The structures found to be rich in phosphatase were periosteum, osteoblasts, osteocytes and organic matrix.⁹

It is evident therefore that alkaline phosphatase is in significant concentration in tissues about to be calcified or in tissues undergoing ossification. As the calcification proceeds the alkaline phosphatase diminishes to a point where it can be demonstrated no longer.

CLINICAL SIGNIFICANCE OF ALKALINE PHOSPHATASE

This enzyme acts at an optimum pH of 9 to 10. Its level in the blood serum is usually determined by the Bodansky or the King Armstrong method.

Bodansky Method. 1 cc. of serum is incubated for 1 hr. at 37° C. with 10 cc. of a mixture containing 0.5 per cent of sodium beta-glycerophosphate and 0.424 per cent of Veronal Sodium buffer at a pH of 8.75. The units of phosphatase activity are defined as milligrams of inorganic phosphorus liberated by 100 cc. of serum. The normal range is 1.5 to 4 units in adults and 3 to 13 units in children from 2 to 15 years of age.

King Armstrong Method. 0.5 cc. of serum is incubated at 37.5° C. at pH 8.9 to 9.1 with a mixture of 0.005 M disodium phenyl phosphate in 0.05 M Veronal Sodium. The units of phosphatase activity are expressed as the milligrams of phenol liberated by 100 cc. of serum. The normal range is from 3.7 to 13.1 with the average at 9.7. Again higher

levels are expected in children between 2 and 15 than in adults

Elevation of serum alkaline phosphatase is indicative of increased osteoblastic activity in the absence of liver disease or obstructive jaundice. It is of interest that this enzyme is formed outside the liver but is excreted by the liver cell into the bile canaliculi. Therefore anything prohibiting its excretion into the bile may result in a backing up of this substance in the blood.

Low normal to absence of alkaline phosphatase occurs in bone lesions due to mesenchymal defect. Rathbun's case of such severe defect reported absence of alkaline phosphatase as the most significant finding.¹⁰ Clinical conditions (together with representative Bodansky units) in which alkaline phosphatase is consistently increased are as follows:

- 1 Active rickets (20 to 40 units)
- 2 Polycystotic form of Paget's disease (15 to 125 units)
- 3 Hyperparathyroidism (20 to 40 units)
- 4 Osteomalacia in healing phase (20 to 40 units)
- 5 Metastatic osteoblastic cancer involving bone particularly carcinoma of the prostate (5 to 15 units)
- 6 Renal osteitis fibrosa generalisata or secondary hyperparathyroidism group (15 to 40 units)
- 7 Obstructive and hepatocellular varieties of jaundice (9 to 60 units)
- 8 Osteogenesis imperfecta (6 to 30 units)¹¹
- 9 Osteogenic sarcoma (15 to 30 units—sometimes elevated)
10. Multiple eosinophilic granuloma (16 to 22 King Armstrong units)¹²

Conditions in which alkaline phosphatase is lowered in Bodansky units are as follows:

- 1 Scurvy
- 2 Mesenchymal defects (acalcification state) Rathbun¹

ACID PHOSPHATASE

In 1925¹³ an enzyme capable of hydrolyzing hexosediphosphate at a pH of 5 was

discovered. It was approximately 10 years later¹⁴ when the source of this enzyme was found. It was found in large concentrations in the prostate and in appreciable amounts in the testes, the epididymis, the seminal vesicles and the spermatic duct. Shortly thereafter Gutman et al., pointed out the clinical significance of high levels of this enzyme in the blood serum.¹⁵ They reported elevation of blood-serum acid phosphatase in metastatic lesions of prostate to bone. These workers had previously indicated elevations of alkaline phosphatase in osteoblastic lesions.¹⁶

It is well known that prostatic carcinoma metastatic to bone is often very difficult to differentiate from the osteoblastic phase of Paget's disease. Both alkaline and acid phosphatase are high in the metastatic prostate condition but only the alkaline phosphatase is high in the osteoblastic phase of Paget's disease. Therefore this observation has proved of great help in differentiating these two conditions.¹⁷

Later it became apparent that acid phosphatase would appear in excess amounts in the blood serum in metastatic carcinoma of the prostate before x-ray evidence of bone involvement.¹⁸ It is not yet clear as to the exact mechanism responsible for the increase in blood levels of this enzyme in cancer of the prostate.

METHODS OF DETERMINATION

The methods used to determine acid-phosphatase levels in blood serum differ from those described above for alkaline phosphatase only as to the substrate and the buffer. It must be remembered that human red blood cells contain a high acid phosphatase concentration and hemolyzed blood cannot be used.

The Gutman and the King Armstrong methods are similar. They employ phenyl phosphate as a substrate and Veronal Sodium as a buffer. The normal values are 0.6 to 2 units per 100 cc. of serum for Gutman, 1 to 5 units for King Armstrong.

The Bodansky method employs sodium beta glycerophosphate as a substrate and

hydrochloric or acetic acid as a buffer. The normal values are 0.1 to 0.4 unit per 100 cc. of blood serum.

PHOSPHATASE IN LEUKOCYTES

Striking differences in levels of phosphatase activity are found in healthy leukocytes

and chronic myelocytic leukemia. In quantitative studies of isolated leukocytes Valentine and Beck find in general, high alkaline-normal acid phosphatase levels with leukocytosis and low alkaline-normal to high acid phosphatase levels with chronic myelocytic leukemia.¹¹

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Hormones as Related to Bone

INTRODUCTION

The endocrine glands elaborate substances usually stimulating called hormones. These glands have no ducts and their secretions are fed directly into the blood stream. The endocrines are referred to therefore as ductless glands. These glands are part of an interacting system—one gland may affect one or all of the others. Furthermore the active substance secreted by one gland may affect a chain of glands resulting in the elaboration by another gland of a hormone that suppresses the original secretion responsible for the entire chain reaction.

Hormones are essential to life. They affect growth, male and female characteristics and the metabolism of carbohydrates, proteins, fats and minerals. Types of people may well reflect a particular hormone balance. Furthermore it is possible that a particular hormone pattern may be inherited.

Keen observers laid the foundation for endocrine study by observing a symptom complex that could be correlated by post mortem study with changes in an endocrine gland. For example Addison recognized certain symptoms and signs during life that could be correlated with changes in the adrenals observed at necropsy.

A second general method in endocrine research has been the surgical removal of a gland or its loss by disease, with observation of the resulting changes.

A third approach has been the study and the chemical analysis of the glands and their secretions in an effort to isolate active principles elaborated by them. Active extracts were thus obtained. These extracts were at first crude and mixed with many other substances. With time, technique improved and

purer forms of the hormones were obtained.

Finally the active principles of glands were identified and synthesized in part or in whole. The effectiveness of a hormone could of course be proved in two ways: (1) by its administration to a patient who showed a symptom-complex indicating deficiency of a particular hormone, an example being the effect of cortisone in the control of Addison's disease; (2) by the administration of the material to an animal whose gland had previously been extirpated. Removal of the gland produced the symptom-complex; treatment with the active principle controlled the symptom-complex. So the cause-and-effect relationship was established. In general, loss of a gland produces a symptom-complex. If the hormone of the gland controls the symptoms, we have both demonstrated an active, effective extract and secondly proved the function of the gland in the organism.

THE ADRENAL

History. In 1855¹ with brilliant clarity Thomas Addison described a clinical syndrome embodying a bronzing of the skin, feeble heart action, irritable stomach, general languor, debility and severe anemia. He observed that this was associated with disease of the adrenal (suprarenal) glands. Brown-Séquard² showed that the removal of the adrenal glands from experimental animals was always fatal. Other workers gradually differentiated the cortex from the medulla and showed that it was the cortex which was essential to life.

Embryology. The cortex is developed from mesodermal tissue, the medulla from ectoderm. The medullary part arises from the sympathetic nervous system, which is

derived from the epiblast. In this the cells are arranged in an irregular manner around the intercommunicating blood sinuses and the sinusoids with which it is richly supplied. A rich lymphatic network is also present. The cells in the medullary part vary in shape and contain granules. Because of this reaction these cells are referred to as chromophil cells. The staining is due to epinephrine which is the active principle of the medulla.

The cortical part of the gland is developed from the mesoblast. In this the epithelial cells are arranged in different zones named (from without inward) the zona glomerulosa, the zona fasciculata and the zona reticulata.

Nervous control of the gland is sympathetic for the medulla which functions as a modified sympathetic gland and parasympathetic for the cortex. The fact that the parasympathetic nerve fibers have only vascular connections none directly with the gland, suggests that any nervous control of the adrenal cortical secretion probably is exercised through the blood vessels.

MacFarland² demonstrated that cortical activity is not under direct neural control whereas the medulla is innervated by secreting fibers. His method was a transplantation of normal denervated adrenals into 95 mature albino rats.

Reaction to Environmental Effects, Stress and Strain, Heat and Cold, Physical Exercise. It has long been observed that an enormous amount of blood passes through the adrenal gland. Addison¹ recognized this as a sign of the great importance of this organ. As knowledge of the endocrines has increased adrenal cortical function has become recognized as extremely complex. Its secretions have opened the door upon a vista of great therapeutic potential.

Addison's¹ observation of the effect of total destruction of the adrenal by tuberculous disease was a great contribution from the clinical viewpoint and has left nothing to be added to this day. It was much later however before the adrenal causation of

Cushing's syndrome a condition nearly the antithesis of Addison's disease was recognized.⁴ Even then the entity had been observed for years although falsely attributed to the pituitary gland.⁵

With passing time and experience the adrenal gland was demonstrated to be closely related to many other glands and to be affected by them and by the environment.

ENVIRONMENT AND TEMPERATURE. In 1937 Selye⁶ and in 1940 Emery and Schwabe⁶ observed increase in the size of the adrenal upon prolonged exposure to cold. Burnstein⁷ observed that the lipid content of the adrenal increased in summer and decreased in winter. This inferred greater activity of the gland in the winter. Further work led to the observation that the structure allowed humans as well as animals to withstand acute environmental stresses. Other stimuli producing adrenal cortical enlargement are oxygen deficiency, thiamine deficiency and toxic substances. Atrophy of the cortex occurs in chronic inanition.

Relationship to Other Glands. THE THYROID. In 1910 Hoskins⁸ observed that the thyroid was one of the most active stimulants of the adrenal cortex. Enlargement of the cortex follows the administration of thyroid whereas thyroidectomy produces cortical atrophy. Of course it may be that the thyroid acts because of the adrenal and not vice versa, but a relationship is clear. Thyroid-adrenal relationship⁹ has been pointed out in coincidence of hyperthyroidism and Addison's disease.

THE PITUITARY. It appears that a most interesting cross-reaction and stimulus of one part of the adrenal by another also occurs. In this way the pituitary gland is brought in as a stimulating factor for the adrenal. Increase in epinephrine a product of the medulla seemingly stimulates the hypothalamus which in turn affects the pituitary. The effect upon the pituitary results in increased ACTH output which stimulates the cortex to produce cortisone.

Adrenocorticotrophic hormone regulates the

structure and the function of the cortex. If the pituitary is removed the cortex atrophies. If ACTH is given the adrenal produces cortisone in increased quantity.

KNOWN SECRETIONS AND METHODS OF STIMULATION

Medulla

Abel¹⁰ proposed the name epinephrine for the vasoconstricting principle of the medulla. In 1894 Oliver and Schäfer¹¹ first prepared an active extract of the medullary tissue. Stoltz¹² and Dakin¹³ were the first to synthesize this substance.

Epinephrine is inactivated by enzymes such as tyrosine and catechol oxidase. Its effect on the various tissues is similar to that obtained by stimulation of the sympathetic nervous system. Elliott¹⁴ observed that an injection of epinephrine into an animal produced a response in the animal's glands or muscles precisely like that of stimulation of sympathetic fibers. He concluded that nerve endings in the muscles or the glands therefore would produce a substance similar to that of epinephrine when they were stimulated.

Dale¹⁵ demonstrated that stimulation of the parasympathetic system caused production of acetylcholine at the postganglionic endings. The lower thoracic sympathetic chains form an adrenalinlike substance at the postganglionic endings. It is closely related to adrenalin and is called sympathin.¹⁶

Cannon and Rosenblueth¹⁶ showed that such a substance was formed at the endings of sympathetic nerves when the nerves were stimulated. It was not precisely epinephrine but similar in action and was termed sympathin. There were two forms. The first form was sympathin E which stimulates nerve endings that cause muscles to contract. The other sympathin I stimulates nerve endings that cause muscles to relax.

Later what was considered to be pure adrenal medulla extract was found to be composed of two materials, epinephrine and norepinephrine.¹ It is possible that the

latter hormone is a precursor of epinephrine. For practical purposes their actions are so much alike that the adrenal medullary hormone can be considered to be epinephrine.

Cortex

Functions. It has long been apparent that the cortex has been the storehouse of adrenal secretions capable of producing the most widespread effects. The steroids are the most important factors elaborated by the adrenal and more than 25 of them have been isolated in chemically pure state. Among these are estrone, progesterone and at least 5 steroids effective in the replacement of cortical function. Physiologically and chemically these latter adrenal cortical steroids may be divided into two groups: (1) the one affecting sodium and potassium levels in the body is represented by 11 desoxycorticosterone and (2) the "S" or sugar hormone group: 17 hydroxy 11-dehydrocorticosterone (compound E or cortisone) and 17 hydroxycorticosterone (compound F or hydrocortisone).

The chemical structure of all steroids is the sterol nucleus, which is the basic component of many biologically active substances such as bile salts, cardiac glycosides, vitamin D, cholesterol, sex hormones, etc. Highly complicated chemical investigations of adrenal cortical steroids indicate that there are at least 25 such compounds.¹⁷

The suprarenal cortex is found to produce three major effects through the various steroids that it produces.

1 **THE CONTROL OF SODIUM VERSUS POTASSIUM IN THE BODY.** The hormone desoxycorticosterone affects the renal tubules so that water, sodium and chloride are conserved and potassium excreted. This is opposite to the observation that, in Addison's disease, sodium is excreted in the urine and potassium is retained in the blood.

2 **THE "S" OR SUGAR HORMONE GROUP AFFECTS PROTEIN AND CARBOHYDRATE METABOLISM.** This group has a diabetogenic effect even enough to raise the blood sugar and can break down protein and convert it

into carbohydrates. This results in negative nitrogen balance. This group appears to increase gluconeogenesis thereby increasing deposition of glycogen in the liver. The utilization of carbohydrates is decreased and the renal glucose threshold is lowered.

This group of hormones of which cortisone and hydrocortisone appear to be the major and important factors has much influence upon the connective tissue. They control much of the cells' reactions. It appears that the effect of cortisone upon rheumatoid arthritis is one primarily to prevent cell reaction to a toxic substance. That action appears also in its usage to combat allergic response.

It is these hormones that respond in the alarm reaction after injury, heat or cold or stress. They will delay tissue healing and eventually result in possible side-effects even resulting in a complete Cushing's syndrome characterized by (1) buffalo form of obesity confined to face, neck and trunk, (2) hirsutism, (3) hypertension, (4) dusky cyanotic facies, (5) purplish striae distributed on breast and abdomen, (6) weakness, (7) decreased tolerance for sugar, (8) hypoproteinemia, (9) hyperchloremia, (10) polycythemia, (11) erythrocytosis, (12) sexual disturbances.

Röntgenographic Features of Cushing's Syndrome or Cortisone Overdosage (1) Generalized osteoporosis often occurs; this is particularly true of the spine, (2) vertebral ankylosis, (3) kyphosis, (4) shortened stature, (5) rounding of the shoulders, (6) skull changes of osteoporosis seen most often on the frontal and the parietal areas resembling malignancy and (7) spontaneous fractures.

Diagnosis The diagnostic points to be borne in mind aside from the suggestive roentgen data are as follows: (1) characteristic lunate atrophies, (2) obesity distributed mainly on the shoulder girdle, the waist and the abdomen, (3) apple-cheeked coloration of the face with bulging, (4) sexual impotence, (5) petechial hemorrhages and ecchymoses in the skin, (6) increased sys-

tolic and increased diastolic blood pressure.

3 THE ADRENAL GLANDS ARE, AS IS WELL KNOWN, A SOURCE OF ESTROGENIC AND ANDROGENIC HORMONES WHICH HAVE A STIMULATING EFFECT UPON PROTEIN METABOLISM. This group also affects sex variation as clearly observed in adrenal tumors of the secreting type which may develop in the female and produce severe masculinizing effects. As a matter of fact they may have a marked effect upon even the genitalia, so that a condition termed pseudohermaphroditism may result, the difference from true hermaphroditism being that such patients do not have the complete components of both sexes.

Secreting tumors may also develop in the male and have severe feminizing effects. 17 Ketosteroid levels in the urine are mainly from the adrenal.

A relationship between the adrenal cortex and the sex gonads has long been suspected. Indeed as given above they arise from a common embryologic structure. Some of the relationships have been determined recently to be on the basis of adrenal production of androgens and estrogens. This is associated with pseudohermaphroditism, virilism and sexual precocity.

Hypertrophy of the adrenal cortex occurs during pregnancy (guinea pigs in estrus, ovulation in pigeons and after castration in rats). Bilateral adrenalectomy causes serious interference with sexual functions.

Adrenal Cortical Hyperfunction (Hypercorticalism) Effects in the main are (1) sexual-androgenic or estrogenic, (2) diabetic—gluconeogenic and associated metabolic disorder and (3) salt water metabolism.

The effects of clinical hypercorticalism are related to age and sex. They are divisible into (1) pseudohermaphroditism, (2) sexual precocity in childhood, (3) adrenogenital syndrome—after puberty, (4) Cushing's syndrome—after puberty, (5) virilism and (6) feminization of the male after puberty.

Adrenal Cortical Insufficiency This concerns us primarily as it affects metabolism.

of sodium potassium and chlorine through the renal regulation of these ions. This may be likened in a limited way to the para thyroid glands and phosphorus.

Large doses of salt and of sodium bicarbonate have long been known to keep adrenalectomized animals in fairly good condition.¹⁸ Atrophy of the cortex occurs when there is lack of vitamins especially nicotinic acid and in chronic pulmonary tuberculosis; hypothyroidism and Simmonds disease.

ACTH, Cortisone and Hydrocortisone
Cortisone was first isolated from beef adrenal glands in 1935. In 1946 its synthesis was accomplished by using the bile acid desoxycholic acid as a starting point. In 1949 Kendall and Hench¹⁹ reported that cortisone often gave remarkable relief in rheumatoid arthritis and subsequently its effectiveness in a wide variety of conditions has been reported.

The concentration of cortisone and hydrocortisone in the body fluids is maintained by the action of adrenal corticotropic hormone (ACTH). A measure of its activity may be inferred by the rate of delivery of lymphocytes to the circulation. The lymphopenic effect of adrenal cortical steroid is a reflection of lymphocytic dissolution in lymphoid organs. Further relationship to the production of cortisone by adrenal corticotropic hormone is inferred by the observation that in normal human beings ACTH induces an increase in neutrophils, a decrease in lymphocytes and a decrease in eosinophils. Similar treatment for patients with Addison's disease is accompanied by only slight increase in neutrophils without a significant change in lymphocytes or eosinophils. This indicated ACTH effect only through cortisone production. In the Addison's disease state no cortisone production occurs from ACTH stimulus for no adrenal capacity is present.

Conn²⁰ reported that the administration of ACTH to acute gouty arthritis caused a complete remission of symptoms for a number of days. This effect is through cortisone production triggered by the ACTH. If

ACTH or cortisone is stopped after the symptoms of gout are controlled, rapid return of acute symptoms will follow. So colchicine or other modalities such as aspirin, phenylbutazone or Benemid²¹ must be continued.

Cortisone or hydrocortisone favorably alter clinical, histologic, serologic and synovial manifestations of rheumatoid arthritis. The repression of many of these changes may persist so long as the hormone is given in adequate dosage.

METABOLIC EFFECTS OF CORTISONE AND HYDROCORTISONE. Cortisone and hydrocortisone affect protein and carbohydrate metabolism promoting gluconeogenesis, hyperglycemia, glycosuria and negative nitrogen balance. They inhibit the activity of the lymphatic system.

The negative nitrogen balance induced by high-dosage cortisone therapy may delay bone and wound healing.

Cortisone or hydrocortisone cannot rebuild bone nor will they undo the deformities which occur in long standing arthritis.

The effect of cortisone in Addison's disease has been reported frequently. Apparently symptoms can be controlled by 12.5 to 25 mg. of cortisone daily and NaCl, although oral administration of cortisone in conjunction with the use of conventional dosages of desoxycorticosterone acetate in place of salt is effective for patients with chronic adrenal cortical insufficiency.

Cortisone and hydrocortisone suppress the activity of the adrenal cortex, and, if their administration is long-continued, atrophy of the adrenal cortex occurs. The action is reversible, however.

When cortisone or hydrocortisone is administered in the human being over extended periods, it may cause widespread physiologic and metabolic effects resembling those seen in Cushing's syndrome.

ROUTES OF ADMINISTRATION. ACTH is a protein and requires parenteral administration. Cortisone is available in its original parenteral form for intramuscular use and in oral tablets. Hydrocortisone appears to be a metabolic derivative of cortisone and

■ used in lower dosages by mouth, thus reducing toxicity and side effects Hydrocortisone is also used intra-articularly and locally At present writing it has become available for intravenous use in emergency cases

CLINICAL SIDE EFFECTS PRODUCED BY ACTH CORTISONE OR HYDROCORTISONE
(1) Moon facies (2) recession of the temporal hairline (3) acne (4) hypertension (5) decreased tolerance to glucose (6) hirsutism (7) clinical hypopotassemia (8) edema with sodium retention and pigmentation and (9) psychiatric disturbances. These effects are usually reversible with cessation of therapy

Following are precautions and tests that are helpful before and during therapy in guiding the physician as to which hormone and what dosage to use (1) eosinophil test with epinephrine or ACTH before therapy (2) eosinophil counts during therapy (3) serum chlorides in similar manner (4) daily weights (5) daily blood-pressure readings (6) NPN (7) blood sugar (8) CO_2 combining power (9) sodium and potassium and (10) ECG

ACTH cortisone and hydrocortisone are of benefit in

- 1 Panhypopituitarism (ACTH)
- 2 Addison's disease (cortisone or hydrocortisone)
- 3 Rheumatoid arthritis (all)
- 4 Acute alcoholism (all)
- 5 Alcoholic psychosis (all)
- 6 Allergic states (all)
- 7 Status asthmaticus (all)
- 8 Periarthritis nodosa (all)
- 9 Rheumatoid spondylitis (all)
- 10 Still's disease (all)
- 11 Lupus erythematosus (all)
- 12 Acute rheumatic fever (all)
- 13 Protection against postoperative shock (all)
- 14 Severe burns (all)
- 15 Psoriatic arthritis (all)
- 16 Pemphigus (all)
- 17 Periarthritis of the shoulder (all)²¹
- 18 Tennis elbow (local hydrocortisone)²²

ACTH cortisone and hydrocortisone are contra indicated in

- 1 Tuberculosis
- 2 Peptic ulcer
- 3 Cardiovascular disease
- 4 Diabetes mellitus
- 5 Cushing's syndrome
- 6 Osteoporosis

Infections. Response to ACTH cortisone and hydrocortisone in infections is similar They tend to suppress allergic inflammatory response This reduces the formation of new blood channels and thus decreases blood flow which could carry more immune bodies and macrophages Furthermore it is possible that they reduce serum gamma globulin²³⁻²⁴

The hormones do not affect infectious agents. They do decrease the inhibitors to infection When these inhibitors to infection are not transported to the site of infection in adequate amount the infection can well run rampant²⁵

Progressions of lesions in tuberculosis have been reported²⁷

In regard to bacterial infections ACTH cortisone and hydrocortisone enhance susceptibility of tissues to the primary effect of bacterial toxins. Thomas and Mogabgab²⁸ found marked enhancement in rabbits following injection of cortisone

Summary Cortisone hydrocortisone and ACTH may affect bone The metabolic effect is primarily one of osteoporosis There is distinct reduction of osteoblastic activity These hormones also cause protein breakdown with increased nitrogen excretion

Other possible relationships of these substances to osteoporosis may be in the hyperglycemia and the glycosuria so frequently observed as resulting from their action

These hormones are unique in reducing tissue response either on allergic or inflammatory basis This is the usual basis for many of the clinical applications for cortisone hydrocortisone and ACTH In addition the value of cortisone and hydrocortisone for replacement therapy in adrenal deficiencies must be noted

TABLE 3*

AGE	SEXUAL CHARACTERISTICS	STATUS OF HORMONE PRODUCTION
3-7	<i>Infantile</i>	Very small amounts of estrogens and 17-ketoids in urine
	<i>Adolescence</i>	
8	Ovarian follicles display more advanced development. Uterus begins to grow	Urinary excretion of estrogens and 17-ketoids begins to increase
10-11	Budding of breasts Adrenarche (appearance of pubic hair)	Estrogen excretion greatly accelerated
11-12	Remodeling of bony pelvis. Vaginal changes, breasts advance to primary mamma stage Growth of external and internal genitalia greatly accelerated	Gonadotropins become demonstrable in the u Estrogen excretion further augmented, becomes cyclic in character
13-14	Appearance of axillary hair Menarche (first menstrual period, average age 13.5)	
14-15	Puberty (earliest normal pregnancies)	Pregnenolol appears in the urine during the h phase
16-17	End of skeletal growth	

* From Talbot, et al Functional Endocrinology p 308 Cambridge, Mass., Harvard Univ Press, 1952

THE GONADS

Estrogens and androgens are present in both sexes with androgen values in the female of child-bearing age approaching those in the male.¹

The important function of the gonads whether of the androgenic or the estrogenic variety in relation to living bone is in relation to their elaboration of hormones. Such hormones are effective in the development and the maintenance of accessory genital organs and secondary sex characteristics.

THE OVARIES

In the female, the important hormones are estrogen, produced by the follicle and progesterone, produced by the corpus luteum. The initiation and the regulation of the varied ovarian functions are dependent upon hormones secreted by the anterior lobe of the pituitary gland. An excellent table correlating hormone production and sexual differentiation is given by Talbot, et al.² and is reproduced herein.

In childhood the ovaries elaborate very little estrogen. At approximately the age of 11 the pituitary release of gonadotropic

hormone increases markedly stimulates the ovaries to increased estrogen production thereby stimulating genital development. The pituitary secretion of gonadotropic cyclic thereby producing cyclic variation in estrogen production. Eventually when the level is sufficiently high menstruation occurs.

Ovarian disturbances (1) Fibrocystic disease (2) primary hypothalamic infarct (3) destructive lesion—Froehle syndrome and (4) congenital defect Laurence-Moon Biedl syndrome.

Estrogen affects bone. Postmenopausal osteoporosis so well described by Albright is a clear-cut entity. It is an osteoporosis state clearly associated with a deficiency of estrogen in the postmenopausal period.

Estrogen stimulates endosteal bone formation and inhibits bone resorption when given in toxic doses in mice.³ A similar reaction was not observed in rats where there was only decreased destruction.⁴ Prolonged administration of estrogens produced phenomena similar to those of osteitis fibrosa.

In 1945⁵ in experiments on wild ducks and pigeons it was found that the local implantation of female sex hormone in either oily or crystalline form, into a long bone

duced localized medullary ossification at site of the deposit. The authors concluded that this resulted from direct local action of folliculin upon skeletal structure. Sex hormones apparently induce epiphyseal closure associated with sex maturity longitudinal growth, although partially inhibited by the gonads can occur when sex hormones are absent. So open epiphyses at the time of sexual maturity may indicate true hypogonadism and this pattern can be considered to be pathognomonic of primary hypogonadism. However in the hypogonad giant of true type it is obvious that overgrowth occurs because of excessive growth not because of an excessively rapid rate of growth. The delay in epiphyseal closure means that growth continues if other stimulating factors for growth are present. This is in contrast with the pituitary giant, in whom the growth rate is excessively rapid. In hypogonadism unclosed epiphyseal plates with active growth may be demonstrated as late as 25 to 30 years of age.

X-ray studies of primary prepuberal hypogonadism show (1) a tendency to long bone growth (2) delayed epiphyseal closure (3) subcalcification, (4) thinning of the cortical layer (5) thin walled normal sized trabeculation and (6) roughening of the metaphyseal margin of growing bone.

Estrogen and growth hormone both accelerate skeletal aging in growing animals but they accomplish this effect in different ways. The pituitary growth principle stimulates growth and hastens epiphyseal-diaphyseal union by inducing premature regression and reabsorption of the epiphyseal cartilage. Estrogen inhibits reabsorption of bone and promotes hyalinization of marrow. Since these hormones modify each other and to a degree oppose each other in cartilage growth effects they have been used with some success in arresting pituitary gigantism.⁷

THE TESTES

These glands are responsible for the formation of sperm and the maintenance of

the secondary sex characteristics. Hormones from this gland furthermore have a wide spread effect upon the whole body. Sperm are produced by the testicular tubules and the masculinizing hormone is produced by the interstitial cells of Leydig.

Embryologically, the testes and the adrenal cortices arise from adjacent structures near the mesonephros in the genital ridge. Therefore it is reasonable to assume that this is a fact—that hormones produced by the interstitial cells of the testicle may have physiologic actions similar to those of hormones produced by certain adrenocortical cells. The testicle as is the ovary is dependent upon gonad stimulating hormones from the anterior pituitary for both development and function.

Human testicular androgen is metabolized and secreted in the urine as neutral 17 ketosteroids. This is a similar situation in regard to the bull from whose testes testosterone has been isolated.⁸ Testosterone enhances nitrogen anabolism and its effect occurs upon muscles skeleton and other structures as well as sex organs.⁹ Testosterone also causes retention of sodium potassium chloride and nitrogen. Such an effect upon nitrogen obviously contributes to its anabolic effect upon protein. This protein storing effect is so marked that when excess testosterone is present, only carbohydrate and fats will be broken down for the energy requirements of the body. Normally without excess testosterone protein is metabolized.¹⁰ At times the serum-potassium level may fall on testosterone the presumption being that it stimulates cells to store potassium, and such storage has been observed.

Because of anabolic protein effect, androgen produces an appreciable increase in musculature. Skeletal growth promoting effect is related also to protein anabolic effect. Androgens accelerate epiphyseal calcification and closure.¹¹ Accelerated maturation may occur on relatively small doses of testosterone but experience with children on androgen indicates that evidence on bone x ray may lag 6 to 12 months.¹²

Testosterone production is of course enhanced by the pituitary through LH or luteinizing hormone whereas the FSH (follicle stimulating hormone) stimulates the ovary to develop graafian follicles and estrogens. The latter in the male stimulate spermatid tubule development and spermatogenesis but not androgen production. In the male therefore LH is referred to as the interstitial-cell-stimulating hormone (ICSH).

Chorionic gonadotropin has action similar to that of ICSH and may be used as a substitute stimulant. Testosterone suppresses urinary 17 ketosteroids and 11 17-oxy corticosteroids apparently by inhibiting adrenocorticotrophic hormone secretion.¹¹

Summary Important factors in relation to bone testosterone obviously accelerates not only bone growth but also skeletal maturation. When testosterone was given to dwarfed children it was observed that 5 mg of methyltestosterone daily was as effective as up to 30 mg daily. The effect was evident within 3 months after onset of treatment.

Accelerated skeletal maturation became evident within 6 to 12 months. Comparison of heights of testosterone fed children with the normal for that age group indicated that in two thirds of the cases testosterone caused a relatively greater increase in the rate of skeletal maturation than in linear growth.¹² This infers of course that an early spurt of growth may be expected with this hormone but the long range effect is to accelerate skeletal maturation with fusion of epiphysis and cessation of linear growth, so that ultimately there may be less stature.¹³

Testosterone causes anabolism of protein even in debility and in the presence of inadequate caloric intake. This may conserve protein at the expense of carbohydrate and fats.

It is argued that it is better not to use this hormone in debilitated states but to raise the caloric and the general nutritional intake rather than to use this modality. It is the authors belief however that in de-

bilitated old age states and in certain severe post traumatic or postoperative states it is wise to use testosterone for its anabolic effect—indeed in numbers of the authors cases it has proved to be lifesaving.

THE PANCREAS

In relation to living bone pancreatic function is indirect. The relationship is on the basis of the effect of the pancreatic "juices" and the secretions of the islet tissue. The pancreatic enzymes affect protein digestion and affect the ultimate absorption of these vital ingredients so necessary to bone structure.

The islet tissue is associated with proper utilization of glucose and hexosephosphates are most important as a source of phosphorus for calcification of bone matrix.

THE PARATHYROIDS

Introduction. The parathyroid glands are so named because they are located about the thyroid gland. They are approximately 4 in number in man although more have been observed.¹ The superior parathyroid glands with the thyroid evolve from the pharyngeal pouches of the fourth branchial cleft. They may vary in location therefore between the superior border of the larynx and the inferior pole of the thyroid.

The inferior parathyroid glands evolve with the thymus from the third branchial cleft. Therefore these glands may be found even deep in the mediastinum.

Parathyroid glands vary in size the largest normal² has been observed at 15 mm long the greatest width at 8.5 mm and the greatest thickness at 3.5 mm. Ordinarily they do not exceed 10 mm by 5 mm in size. However the fact that normal glands of increased size do occur means caution in interpretation of pathologic state. The glands are flattened and ovoid in shape. When fresh they are yellow brown in color. They are covered with a thin capsule which penetrates the gland although it does not divide it into lobulations.

In 1880 the superior parathyroids were described³ and differentiated histologically from thyroid tissue. This author Sandström also credited description of these glands to Remak in 1858 and Virchow in 1860.

In 1895 the inferior parathyroids were described.⁴ It was considered for a long while that hyperplasia⁵ of the parathyroids was the result of osteomalacic processes. This thought was gradually discarded however starting particularly with MacCallum in 1908⁶ who described a rapid drop in serum calcium after parathyroidectomy and tetany whenever the serum calcium fell below a critical value. Further development of the modern concept of parathyroid action followed with the isolation of parathyroid hormone (parathormone).

Parathyroid hormone as now used was isolated by Collip in 1925.⁷ In 1926⁸ Mandl removed a parathyroid adenoma with improvement in hyperparathyroidism then known as von Recklinghausen's disease. From then on the concept of the function of the parathyroids and of calcium metabolism became clearer.

Histology. There has been much discussion about the type of secretory cell and whether or not more than one hormonal substance may be elaborated by this gland.

Part of the confusion results because of different staining characteristics of the cells and the possible existence of various stages in the differentiation of the principal or chief cell.

Up to about the age of approximately 10⁹ there is apparently only one uniform type of cell which is therefore termed the principal cell. These principal or chief cells have no granules in their cytoplasm and may vary from nearly clear to dark staining cells. Some are spoken of therefore, as dark chief cells some as light, and some as clear chief cells. A reasonable hypothesis¹⁰ is that the variation in staining characteristics may be simply different stages in a secretory cycle.

As the child approaches puberty other cells are found in the gland. There appear to be transitions from chief cells. These cells are larger, occur in clumps and contain

granules in their cytoplasm. These cells are acid-staining and are referred to as oxyphilic cells. These are nearly unique in man and no particular secretion has yet been related to them.

Physiology. The parathyroid gland secretes a protein or a protein linked hormone. There may be two active forms since ultracentrifuge studies indicate two different molecules, one of a molecular weight of 20,000 the other approximately 500,000.¹¹

Only one clearly active hormone has been identified from the parathyroid, yet the possibility that two hormones may be elaborated is present. The arguments in favor of this are the two distinct types of cells and the reaction of these cells to varied stimuli.

This hormone has functions, many of which have been clarified but some of which are still controversial and some of which may well be unknown.

1 It maintains the blood-calcium level. Stated another way its withdrawal is associated with a blood-calcium fall. When it is in excess it causes a blood-calcium elevation. Normal parathyroid function prevents tetany.

2 It lowers the blood phosphorus level.

3 It increases diuresis of both phosphorus and calcium first of phosphorus and later of calcium. This is accomplished by the inhibition of reabsorption of phosphorus from the glomerular filtrate by the kidney tubules (Fig 16 Section C).

4 It produces osteoclasts of bone by stimulating osteoclast formation and osteoclast activity.

5 It will produce bone absorption by direct contact of gland to bone even without evidence of induced osteoclast activity.¹² Shortly after the injection of toxic amounts of parathyroid hormone into rats there is observed a breakdown of bone particularly of the spongiosa of the metaphysis. The very first stage of this before the 9 to 12 hour stage appears to be a humeral reaction because osteoclasts are not mobilized until after 9 to 12 hours and of course then are prominently observed in the areas of bone destruction.¹³ This work indicates clearly

that the parathyroid produces reabsorption of bone by direct action aside from any induced cellular effect.

6 It inhibits the calcifying effect of vitamin D

7 According to Shelling¹² it increases the solubility of phosphorus and calcium so as to maintain these substances in ion form beyond their expected solubilities as determined from the solubility constant. Body fluids are approximately saturated in relation to calcium and phosphorus salts. So if the pH remains constant, a rise in calcium ions will result in a fall of phosphorus ions and vice versa.

McLean showed that rachitic cartilage when placed in serum of an animal made hyperparathyroid by injections of the hormone took up bone salts more readily than when placed in serum from a normal animal. The conclusion is that parathyroid hormone leads to supersaturation of blood with respect to calcium and phosphorus.¹⁴ This varies from the thesis that the primary effect of parathyroid hormone is phosphorus diuresis which leads to undersaturation.¹⁵

There has been much work in regard to the tie up of parathyroid hormone to calcium. MacCallum's⁶ original classic research clearly indicated critical calcium levels. When the calcium dropped below this in parathyroidectomized organisms there was tetany. Through countless researches since that time it has been shown that if the calcium level is not maintained death ensues.

However, there is a correlation in values of calcium and phosphorus that is relatively constant. When total serum calcium to serum phosphorus is expressed in mg/100 cc., their product remains constant. In normal states the proportion is roughly 4 of phosphorus to 10 of calcium. If the calcium is low the phosphorus is usually high. If the product of both calcium and phosphorus is 30 or above for adults and 40 to 55 for growing children calcification of matrix will proceed. If below it will not occur.¹⁶ and if in children rickets will be evident. If in adults osteomalacia. Bone inorganic matter

is formed of crystals. These are the result of precipitation by calcium phosphorus, carbonate¹⁷ and other ions.

Much argument as to whether phosphorus or calcium is primarily related to parathyroid hormone has been advanced. There is no argument about the fact that the ionized forms of calcium and of phosphorus are the only ones related to the parathyroid.

Hyperphosphatemic Effect of Parathyroid Hormone. Albright¹⁸ has been a proponent of the relationship between the parathyroid glands and phosphorus; that elevation of serum phosphorus produces hyperparathyroidism and that excess parathyroid hormone causes phosphorus loss because the hormone prevents reabsorption of phosphorus from the kidney tubules. With high blood phosphorus and low blood calcium parathyroid excess occurs. The first effect of injection of parathyroid hormone is increase of urinary phosphorus excretion and lowered blood phosphorus. Later the calcium effect occurs with hypercalcemia and then hypercalcuria.

Parathyroid hormone influences phosphorus through control of reabsorption of glomerular filtrate phosphorus (Fig 16 Section C). When parathyroid hormone is minimal or after parathyroidectomy practically all phosphorus is reabsorbed by the kidney tubules. When hyperparathyroidism occurs as by extract administration the ratio of reabsorbed renal tubular phosphorus to glomerular filtrate phosphorus consistently falls.

When parathyroid action is maximal reabsorption of phosphorus through renal tubules is completely inhibited and the phosphorus in urine equals that filtered by the glomeruli (Fig 16 Section C III and IV).

These relations hold regardless of relatively large changes in serum phosphorus concentration and in absolute values for filtered and reabsorbed phosphorus.

So parathyroid hormone increases when serum phosphorus concentration rises. When serum phosphorus falls parathyroid hor-

monium decreases. When phosphorus intake increases hyperparathyroidism occurs. Control is at the kidney tubules. When dietary phosphorus is below 300 mg. per 100 lbs. of body weight per day hypophosphatemia may occur. When it is above 6 000 mg. per 100 lbs. of body weight per day hyperphosphatemia may develop.

Whenever a condition is present in which the blood-phosphorus level becomes elevated, there is at once a stimulus to increased parathyroid hormone secretion. The same effect is never true with regard to calcium. This condition is exemplified in two forms of rickets. Simple infantile rickets with high-calcium, low-phosphorus levels in the serum is never associated with parathyroid hypertrophy. Low-calcium high-phosphorus rickets is always associated with parathyroid hypertrophy and hypersecretion. In these states there is actual increase in parathyroid hormone in blood above the normal concentration. This the authors have demonstrated by the Bengt Hamilton¹⁹ technique. The authors also have observed it in monkeys in which high-phosphorus low calcium and low vitamin D intake was carried out.

The logical conclusion from this would be that parathyroid hormone acts primarily upon phosphorus and that the lowering of serum phosphorus causes a relative increase of calcium by some still not fully understood disturbance of their relationship.

Hypocalcemic Effect of Parathyroid Hormone. Others have concluded that its effect is primarily upon calcium and that hypocalcemia is the primary stimulus for the gland. It is also stated that, when levels of both calcium and phosphorus are high in the blood no hyperparathyroidism occurs; that parathyroid hormone increases calcium level in blood and stimulates blood to take up calcium; and that then the reciprocal relationship to phosphorus occurs.

The mechanism by which parathyroid hormone influences serum calcium is still controversial. One theory holds that injection of this hormone directly stimulates

destruction of bone. The calcium thus released enters the blood stream to maintain or restore the serum-calcium level.¹⁴

The second idea is that the parathyroid hormone directly causes affinity of the blood for calcium. Osteoclastic activity is a secondary effect destroying bone to yield calcium for the mineral hungry serum. Evidence for this thought has been adduced by Ham and Scholl¹ who found retardation of dentin calcification in the incisors of growing rats without osteoclastic proliferation in the presence of elevated blood-calcium levels following parathyroid hormone administration.

The third consideration is a kidney mechanism in which hypocalcemia is supposed to induce increased renal tubular reabsorption of calcium and thus conserve the mineral¹⁶ (Fig 16 Section D).

Summary of Parathyroid Hormone Action. It must be remembered that when the calcium is lowered the phosphorus is relatively elevated. Whether the primary effect is associated with an elevation of calcium or lowering of phosphorus is not really too important. A concept of parathyroid hormone effect that fits normal and abnormal states will work on either side. We know that elevation of blood phosphorus increases parathyroid secretion; that relative lowering of blood calcium produces parathyroid hypersecretion; that parathyroid hormone increases osteoclast formation and osteoclasia; and that parathyroid gland simply by contact with living bone will produce absorption of bone without the presence of osteoclasts. The elaboration of parathyroid hormone can be explained as a response either to lowered blood-serum concentration of ionized calcium or to elevated serum concentration of soluble phosphorus.

Parathyroid hormone also produces direct effects upon calcium and phosphorus as in primary secreting adenoma.

We may consider the parathyroids as a part of a closed system. That system is like the four corners of a square: first the parathyroid, second the kidney, third calcium

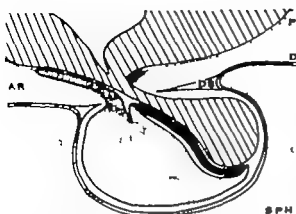


FIG 15 Diagram of a sagittal section of the hypophysis cerebri showing the relation of the pars tuberalis to the meninges. Lines brain floor and pars nervosa fine stipple pars anterior coarse stipple pars tuberalis solid black pars intermedia SPH sphenoid bone I pia mater D dura mater DS, diaphragma sellae AR, arachnoid spaces (From Atwell W J Am J Anat. 37 174)

fourth phosphorus Each of these components affects and is affected by any or all of the others

Tubule renal calcium reabsorption falls as the phosphorus rises. Yet when parathyroid excess occurs as a result of increased phosphorus intake the tubular reabsorption of phosphorus is reduced so phosphorus is lost Yet in this instance the tubular calcium reabsorption changes little This suggests therefore possibly two active parathyroid hormone factors one regulating tubular calcium reabsorption and the other tubular phosphorus reabsorption. If this is so these principles of parathyroid hormone must be secreted at varying independent rates according to need

If calcium intake is varied high to low with phosphorus constant serum calcium falls only slightly and urinary calcium excretion drops to very low levels Parathyroid glands of these animals show variation in gland size inversely related to calcium intake.²⁰

After parathyroidectomy calcium in serum will drop when the calcium intake is

restricted Parathyroid hormone will boost the lowered calcium in serum toward normal, by decreasing calcium tubular excretion.¹⁸ All this indicates that either hypocalcemia or hyperphosphatemia prompts increased parathyroid secretion

So to repeat either postulate—(1) that the parathyroids primarily maintain blood calcium level or (2) that the parathyroids primarily control blood phosphorus level—is tenable That there are two not necessarily interrelated parathyroid hormone factors is possible The thought that one is primarily a calcium mechanism the other a phosphorus mechanism could explain their seeming confusion.

Relationship of the Parathyroids to Other Endocrines. Other glands may affect the parathyroids but do so in indirect fashion, as pituitary through growth factor thyroid through stimulation of metabolism.

Parathyroid-gland enlargement is observed regularly in pregnancy²¹ in acromegaly⁸ and in eosinophilic adenomas of the pituitary²²

The parathyroids are quiescent unless stimulated by high phosphorus or low-calcium intake If a high-calcium and low-phosphorus diet is given to parathyroid ectomized animals they may survive for long periods.

The primary effect physiologically to increase parathyroid activity is hyperphosphatemia or hypocalcemia. No convincing evidence of the effect of other glands has been presented.⁸⁻²³ Parathyroid hyperplasia has been induced experimentally by administration of anterior pituitary extracts,²⁴ and involution has occurred in experimental hypophysectomy

THE PITUITARY

The pituitary or hypophysis cerebri is located on the upper surface of the sphenoid bone and lies just under the brain to the base of which it is attached by the pituitary stalk.¹ It measures 1.5 cm. in the transverse plane 1 cm. in the sagittal plane and from

TABLE 4 PARTS OF THE HYPOPHYSIS AND THEIR EMBRYOLOGIC ORIGIN

MAIN LOBES	COMPONENT DIVISIONS	ORIGIN
Pars tuberalis	Pars tuberalis	Oral ectoderm
Anterior hypophysis (anterior lobe pars anterior pars rhomboidalis, pars distalis)	Anterior hypophysis	
Posterior hypophysis (posterior lobe pars posterior)	Intermediate lobe (pars intermedia)	Brain
	Neural lobe (pars nervosa, infundibular process)	

Reproduced by permission from Smith, et al. *Halley's Text Book of Histology* p. 611 ed. 10 Baltimore: Williams & Wilkins, 1940

0.5 to 0.75 cm in thickness.² It is enveloped by the dura mater and is so well protected that Cushing likened it to the nugget in the innermost of a series of Chinese boxes and suggested that this indicated it was of great importance.

The pituitary is separated into two main sections (Fig. 15). The first is that part that is anterior to the cleft in a child or to a row of follicles which replaces the cleft in an adult and is referred to as the pars anterior. The area behind this is called the pars posterior. Between these two are the pars intermedia and the pars tuberalis.

Embryology. The pars anterior, the pars tuberalis and the pars intermedia develop from an epithelial surface as do endocrine glands in general and on microscopic examination show a rather typical endocrine gland characteristic. The pars nervosa or pars posterior develops from the base of the brain. It fits into a concavity in the pars anterior separated from the latter by the pars intermedia. The pars anterior forms from Rathke's pouch which is an ectodermal bulge extending from the roof of the oral fossa. This ectoderm proliferates and extends toward the anterior surface of the floor of the brain. An additional upward extension becomes the pars tuberalis. The posterior wall becomes the pars intermedia. This pars intermedia joins with the pars nervosa to form the posterior lobe. A residuum of cells like those of the pars anterior may remain in the pharynx from which the anterior lobe develops. When it is present it is called the pharyngeal hypophysis.

Histology. The glandular cells of the pars

anterior are of two types: *chromophobes* and *chromophils*. These are present in approximately equal numbers. These cells appear to be of common origin but in different stages of transition.

1. The chromophobes take up stain poorly; the chromophils take up stain well.

2. The chromophobes are smaller than the chromophils and tend to show as a nesting or a grouping.

3. 75 per cent of the chromophils are acidophilic and are therefore called acidophils. About 25 per cent of these cells are basophilic.

4. The routine hematoxylin and eosin stains distinguish the acidophils from the basophils because the former are pinkish and the latter are from purple red to bluish. Furthermore, the basophils are in greater numbers at the periphery of the gland.

5. It appears that cells can transmute from chromophils to chromophobes or vice versa, although there are some who are of the opinion that there may be two types of chromophobes—one which may become an acidophil and one which may become a basophil.³

The nuclei of these cells vary considerably in their ability to take up stain. This may infer different stages in the secretory cycle.^{2,3} Severinghaus thinks the cells accumulate granules and become darker thereby. They then discharge the granules and become lighter. Thus the lighter cells are probably beginning to accumulate granules and the darker ones are beginning to discharge them.

Apparently more than a single hormone

arises from the pars anterior because there are numerous effects from the material from this portion of the pituitary gland. At least four pure hormones have been isolated and others may be found in the future. The hormones apparently are secreted by the acidophils and the basophils.² No hormonal imbalance occurs in conditions in which chromophobe cells are greatly increased. Severe hormone-balance disturbance does occur when there is overgrowth of acidophils or basophils.

Collip⁴ some years ago noted that certain fractions of the crude extract produced several different effects. He thought therefore that the gland produced only three basic hormones which had different effects because of changes in their final chemical structure when they were secreted.

The three important factors elaborated by the anterior pituitary are (1) growth hormone (2) lactogenic hormone and (3) tropic hormones subdivided into (a) thyrotropin (b) adrenocorticotropin, (c) gonadotropin and (d) some indirect effect upon parathyroid and pancreas.

GROWTH HORMONE

Removal of the pituitary gland stops growth which is resumed if extracts of pars anterior are given. Extracts of the pars anterior affect growth of the body as a whole but the greatest effect is upon the cartilage cells in the epiphyseal plate of the long bones. These cells continue to divide when anterior-pituitary activity is present; they stop dividing when it is absent. So in the absence of this growth factor this zone of maturation of bone does not continue to increase in thickness. Calcification of the plate however will continue. The epiphyseal plate becomes markedly thin and growth will stop.⁵

Conversely if there is a growing individual whose epiphyseal plates have not yet been replaced by bone and active growth hormone is given, growth will continue as long as this growth hormone is available. Indeed in individuals in whom abnormal growth of acidophils or an acidophilic tumor

occurs the state of gigantism can result. This of course means that growth can continue until 20 or 30 years of age.

The longitudinal growth continues because cartilage cells continue to proliferate in the epiphyseal plates. If the epiphyseal plates have been replaced by bone then the longitudinal growth no longer can occur. If an acidophilic tumor develops it does not materially affect the longitudinal growth. It will affect areas of membranous bone formation, such as the terminal phalanges of the fingers and the toes, which will show tufting; the mandible which becomes markedly enlarged (prognathism); the vault of the skull which enlarges considerably. It is of interest too that there is a limited reactivation of endochondral bone growth and periosteal proliferative reaction at the vertebral bodies and the costochondral junctions of the ribs. This condition is referred to as acromegaly.

Hypopituitarism. This is associated with excessively rapid calcification of the epiphyseal plate. This results because cartilage-cell proliferation is reduced when hormone output is reduced. These patients show gnomelike round faces, striated obese growth, index fingers longer than the third fingers, disturbance of the epiphyseal lines of the bones.

LACTOGENIC HORMONE

This is also called prolactin. White⁶ prepared it in crystalline form. It causes the mammary glands of the female to grow and develop so that they may secrete adequate supplies of milk. It also produces a maternal attitude even in males. Furthermore, this gland increases epithelial proliferation of the lining of the crop gland in the fowl since they feed their young in part with this material. This effect provides an accurate method for a biologic assay of this hormone.

TROPIC HORMONES

These hormones stimulate the growth and the function of other endocrine glands and for that reason are referred to as tropic

hormones. The four tropic hormones so named because of the particular gland that they affect are (1) thyrotropin which affects the thyroid (2) adrenocorticotropin which affects the adrenal gland (3) gonadotropin which affects the gonads (4) the *pars intermedia* which affects the pancreas and possibly the parathyroid also. It is possible that the *pars intermedia* action may occur indirectly through other hormones involving or affecting other glands. For example the effect upon parathyroid occurs possibly through the effect of the growth hormone.

The reaction and the interaction of one endocrine upon another is exemplified best by the pituitary which appears to be the controlling gland. The pituitary works through tropic hormones which stimulate other glands to function. The hormones secreted by these other glands in turn reduce the output of the original tropic hormones by the pituitary. For instance if the thyroid gland is producing too little thyroxin thyrotropin is secreted in extra amounts. The thyroid gland therefore increases its output of thyroxin. If the blood level of thyroxin becomes excessive then it will reduce the output of pituitary thyrotropic hormone. The reduced amount of thyrotropic hormone will then reduce the secretion of thyroxin by the thyroid gland.

It would appear that the pituitary is constantly running a quantitative analysis of the blood levels of the various hormones whose production it controls via the tropic hormones. It works by releasing stimulating hormones when the level of a particular hormone drops below the required level.

This is summed up as the "push pull theory." The theory in general terms is that a tropic hormone is secreted by the *pars anterior* if the level of a hormone elaborated

by another gland falls below normal. If this gland secretes to above normal then the tropic hormone production of the pituitary is suppressed.

Although the growth hormone is not basically a tropic hormone its concentration is related to sex hormones. A high concentration of female sex hormones will suppress the secretion of the growth hormone as well as of the lactogenic hormone.

The relationship of the sex hormones to the gonadotropic ones is exemplified by a high level of female sex hormone which will suppress gonadotropic hormone secretion. If the sex glands are extirpated and the sex hormone blood level becomes reduced then continual increase in gonadotropic hormone by the *pars anterior* occurs. This level may become quite high for in this condition no sex hormone is elaborated to suppress the gonadotropic one. So eventually the pituitary cells responsible for gonadotropin become exhausted or develop vacuoles in the cytoplasm, which can be referred to as castration cells.

The *pars tuberalis* appears to be an extension of the *pars intermedia*, but if it produces a hormone as yet it is not clearly defined. It is better developed in animals than in man, and in certain species it produces a hormone called intermedin which causes the pigment-containing cells of some animals to expand. This permits a change in the color scheme of the organism to blend with its surroundings.

The *pars nervosa* has been known for years to produce a substance which on injection would cause smooth muscles of the body to contract. Hamm² isolated two extremely active fractions from the crude extracts (1) oxytocin and (2) pitocin. Having no specific bone effect they will not be discussed here.

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Vitamins as Related to Bone

VITAMIN A

Vitamin A does not exist as such in plants. Here it is a provitamin carotenoid plant substance which is converted into vitamin A in the animal organism.¹ It appears to be stored in various organs but especially in the liver. There are a number of vitamin A forms. Vitamin A₁ has been synthesized and is found in the liver of salt water fish.² Vitamin A₂ has been found in the eyes the liver and the intestines of fresh-water fish.³ The concentration of pure vitamin A in the livers of certain animals notably the polar bear is so great that it has long been considered toxic by Arctic explorers.

Vitamin A is found most commonly in animal and fish liver egg yolk butter and cream. It is found as provitamin A in vegetables with yellow or green coloring such as carrots yellow corn spinach string beans, green peas and the like. Colorless vegetables contain very little carotene or none at all.

It appears that vitamin A is the form chiefly utilized by the human organism. The unit of vitamin A activity is the international unit (I.U.) which is the same as the U.S.P. unit. The biologic method of unit determination is by measurement of rat growth. The physical methods are either by measurement of ultraviolet absorption at 328 m μ and the physical-chemical method of measuring about 620 m μ the blue color following reaction with antimony trichloride.⁴

The potency of vitamin A is plotted against a standard solution which may vary as much as 25 per cent because of impurities which would interfere with the above methods of standardization. As a result batches of crystalline vitamin A may

vary from 3 000 000 to 4 500 000 I.U. per gram. This of course refers only to synthetic vitamin A. Natural vitamin A standardization is complicated further inasmuch as it occurs in free and esterified forms.

Absorption of vitamin A is dependent upon fat absorption. Furthermore it parallels fat absorption. Therefore an indirect but accurate test for fat absorption is measured by noting the plasma vitamin A curve after ingestion of a standard dose of an oily preparation of vitamin A. After a dose of 5,000 units of vitamin A per kg. of body weight normal adults show a rise in plasma concentration which reaches a maximum of about 1,000 to 3,000 I.U. per 100 cc. of plasma. On the other hand the increase in the concentration of plasma vitamin A after this dose in patients with disease of fat absorption is negligible and a relatively flat curve is obtained. However when vitamin A is given in aqueous medium by means of solubilizers the vitamin A absorption is approximately the same in people with diseases of fat absorption as in the normal.

Conversely, conditions in which fat absorption is decreased are accompanied by decreased levels of plasma vitamin A. Such conditions include idiopathic steatorrhea, cystic fibrosis of the pancreas, congenital obstruction of the bile duct, celiac disease, infectious hepatitis and carcinoma of the head of the pancreas. Of course it must be remembered that disease of the liver may affect vitamin A levels from two points of view: first, provitamin carotene is converted into vitamin A in the liver; second, liver disease affects fat absorption if bile production or excretion is affected.

Serum Levels of Vitamin A. The concentration of vitamin A in the blood has been investigated in considerable detail and is

sitive indication for diagnosis of vitamin A deficiency. The plasma is used for determination since there is practically no vitamin A in the red cells. The normal values for vitamin A content of plasma range from the level determined by Merrill (1.5 of 33.2 micrograms per 100 cc., which could be equivalent to 149 I U per 100 cc. for men and 29 micrograms per 100 cc. for women which is equivalent to 131 I U per 100 cc. for women up to levels of 207 I U per 100 cc. reported by Popper and Steigmann.⁶

Excretion. On normal food intake with or without supplementary vitamin A this vitamin is not excreted as such in the urine or in the stool. Total daily excretion on a well balanced diet is about 12 mg. of carotene and 6 mg. of xanthophylls and no vitamin A.⁷ When vitamin A is given in oil⁸ the excretion may be as much as 7 per cent of the injected vitamin A. However, the plasma concentration is much higher when aqueous preparations of vitamin A are used in rats, guinea pigs and infants. It appears fairly definite therefore that aqueous preparations of vitamin A are absorbed more effectively than the oily forms. (By "aqueous preparation" is meant vitamin A dispersed by means of a "wetting agent" in a water-propylene glycol mixture.)

Deficiency of Vitamin A. Lack of vitamin A in the diet of animals prevents growth and leads to atrophy of epithelial cells throughout the body. In addition disturbances of bone growth and of the central nervous system may occur. Vitamin A is essential to the formation of visual purple in the retina and is necessary for vision in dim light.

The chief evidences of vitamin A deficiency in man are impaired ability to see in the dark and the consequences of epithelial-cell atrophy. Dark adaptation for distance in an individual on too low vitamin A is quickly corrected by large doses of vitamin A to supplant it. If the total stores of the body have not reached normal there is a recurrence of symptoms or a relapse

will occur rapidly. If the supplementary vitamin is stopped too soon. Several studies show that the concentration of plasma vitamin A is a more sensitive criterion of vitamin A deficiency than dark adaptation.⁹

In regard to epithelial changes the specific pathologic findings of vitamin A deficiency are found in many epithelial structures and show atrophy of epithelium, reparative proliferation of basal cells and differentiation of the new product into stratified keratinizing epithelium. This means that essentially all mucous membrane becomes converted into epidermis by this keratinizing metaplasia.

Clinically, two skin conditions are found in which there is evidence of vitamin A deficiency: Darier's disease and pityriasis rubra pilaris. These diseases are both characterized by hyperkeratosis of the hair and the sebaceous follicles. In Darier's disease serum vitamin A is normal and dark adaptation is commonly below normal.¹⁰

Hypervitaminosis A. It has been shown that the administration of large doses of vitamin A to young growing rats leads to skeletal fractures and intramuscular hemorrhages and that adult rats may die suddenly from massive hemorrhages in the viscera.

Cases of hypervitaminosis A in children have been reported.¹¹⁻¹⁴ A case of any one of these will illustrate the chief clinical features as they are all similar and similar to those features determined in studies on animals.

Important findings are shown on roentgenograms of long bones which show fragmentation of the distal fibular epiphyses and pronounced periosteal thickening. Hepatomegaly, sparse coarse hair and increased levels of vitamin A in the serum are found.

When excessive intake is discontinued the clinical and the radiographic findings regress.

VITAMIN C

Vitamin C or ascorbic acid is a relatively simple chemical carbohydrate substance first

isolated by Szent Gyorgyi in 1928.¹ It was first crystallized in 1932 by Waugh and King² and synthesized in 1933 by Hirat.³ It is found in citrus fruits, cabbages, berries, turnips, tomatoes, spinach and both green and red peppers. Animal foods are poor sources of this vitamin. However, it is found in human milk in amounts several times that of cow's milk if the mother is on adequate vitamin C.

Vitamin C can be synthesized by plants and by animals such as the rat and the dog. It cannot be synthesized by the guinea pig, the monkey or man. It is water-soluble. Heat, sunlight and oxidation processes easily destroy it. Copper catalyzes the oxidation of this compound and if food containing vitamin C is cooked in a copper container, vitamin C is destroyed still more rapidly.

Man cannot store or synthesize vitamin C. He will absorb this vitamin until tissue saturation is reached. When this occurs, the plasma level will reflect this by a level of approximately 1 mg per 100 cc.

Various tissues have different levels of saturation. The adrenals, for instance, may contain 39 to 58 mg of ascorbic acid per 100 Gm. of tissue.⁴ The red blood cells maintain a level similar to that of plasma. The white blood cells contain a concentration of from 6 to 58 mg per 100 Gm. of white blood cells.⁵ After the saturation level of plasma and tissues has been reached, all excess intake is reflected in excretion through the kidney, since vitamin C is a threshold substance.

Various tolerance tests to measure levels of tissue saturation have been devised. These are based upon the fact that the percentage of an oral dose that is excreted in the urine is a measure of the degree of general tissue saturation. All these tests, of course, imply normal kidney function.

Requirements. Intake levels which yield maximum plasma concentration of ascorbic acid are about 1.5 to 2 mg per kg. A satisfactory intake is that recommended by the Food and Nutrition Board of the National Research Council in 1953. They recommend

for a 65-kg man, 75 mg per day; for a woman of 55 kg., 70 mg per day; for women in the latter half of pregnancy, 100 mg per day; and in lactation, 150 mg per day; for children under 1 year, 30 mg per day; for children aged 1 to 12, 35 to 75 mg per day; for teen-age groups, approximately 80 to 100 mg per day.

If vitamin-C intake is restricted, the plasma level may be maintained while the tissues are being depleted. Obviously, then, single determinations of vitamin-C levels in plasma and urine are not valid, but serial studies are necessary.⁶

Tissues may become depleted through inadequate intake or excess metabolism of vitamin C. The body uses vitamin C in excessive amount under conditions of stress and in fevers.

There appears to be no such thing as overdosage of vitamin C. No toxicity from this vitamin has been reported.

Excretion. This is a threshold substance and is excreted primarily through the urine. The most important factor determining the amount excreted through the urine is the degree of tissue saturation. So if intake level is normal, even slight increases in intake above normal will be excreted. If level has been subnormal and tissues undersaturated, a simple large dose may be largely retained.

Method of Action. It is interesting that, despite a great deal of research work upon vitamin C in man and in experimental animals, the precise *modus operandi* has not been determined. Inferences as to the effects of ascorbic acid may be drawn from observations on clinical and experimentally induced scurvy, with particular comment upon the changes in bone and cartilage that may be observed in vitamin-C deficiencies.

When vitamin C is deficient, fibroblasts, osteoblasts and odontoblasts are unable to manufacture their respective intercellular substances. Therefore, there will be a deficiency of collagen, osteoid and dentin. Bone reflects this effect through absence of matrix formation. Osteoblasts will be present and

even have the capacity to reproduce. They will do no work and form no osteoid.

A measure of this cellular inactivity is as follows:^{1, 2} (1) the absence of alkaline phosphatase as determined on the glycerol phosphate incubation technique; (2) the absence of metachromatic fibers by silver stains; (3) decreased or absent cytochrome oxidase activity; (4) decrease of glycogen in the osteoblast cytoplasm; and (5) decrease of ribose nucleic acid.

Cartilage growth and even calcification of cartilage will continue in scurvy.

It appears that in general the action of vitamin C may be to further the normal development of intercellular ground substance in bone and other connective tissues. All signs and symptoms of vitamin-C deficiency are associated with the disturbances in these areas.

VITAMIN D

Vitamin D is primarily a fat-soluble vitamin. There are 10 substances which have antirachitic activity. The two most important are (1) vitamin D₂ viosterol or calciferol which is the product of irradiated ergosterol and (2) vitamin D₃ which is the product of irradiation of 7-dehydro-cholesterol.

The strength of these substances is measured in international units—1 IU is the biologic activity of 0.025 microgram of pure crystalline vitamin D₂ in 1 mg of olive oil. The biologic activity of vitamin D is measured by its capacity to cause calcification of rachitic rats under standard conditions.

The natural sources of vitamin D are fish-liver oils and the products of ultraviolet irradiation of the cholesterol contained in the intradermal tissue. It is of interest that research has shown that unit for unit cod liver oil concentrates are more effective in antirachitic property than is viosterol.¹

In 1953 the National Research Council Food and Nutrition Board listed the daily requirement of vitamin D as 400 IU for

infants, children and adolescents up to 20. A similar amount is recommended for pregnant and lactating women. It is felt that adults who normally are exposed to sunlight need no additional vitamin D.

Function of Vitamin D. When calcium intake is increased without the addition of vitamin D, fecal calcium and then fecal phosphorus increase. This is due to the formation of insoluble calcium phosphates in the gut which are then excreted.^{2, 3} Conversely, when phosphorus intake is increased without the addition of vitamin D, fecal phosphorus and calcium increase. Again there is precipitation of insoluble calcium phosphates in the gut.^{2, 3}

Vitamin D decreases fecal excretion of calcium and phosphorus.

It appears that the important effect of vitamin D is to increase the absorption of calcium from the gut. This is indicated by the work of Albright upon a patient with idiopathic hypoparathyroidism.⁴ This patient showed no appreciable increase in fecal calcium excretion on 540 mg of calcium intravenously. When the same amount was given by mouth there was a marked increase in fecal calcium excretion. When vitamin D was added and increased oral calcium continued, fecal calcium excretion diminished.

This finding agrees with work on osteomalacia⁵ in adult Chinese in which calcium chloride was retained when given intravenously. Therefore the high fecal excretion of calcium in this condition was the result of lack of absorption, not of re-excretion into the bowel. It is reasonable to consider that phosphorus too, without vitamin D, will increase calcium and phosphorus fecal output. Albright in studies on vitamin D resistant rickets indicated that increased oral or intravenous phosphorus did not increase fecal phosphorus and calcium excretion.⁶ This is not in agreement with others² or with the authors' own work upon osteomalacic monkeys.⁷

In any event, since usual diets maintain reasonable proportions of calcium and phos-

phorus it is not important to be unduly concerned with solitary calcium or solitary phosphorus effect. All that need be considered is Albright's primary contention that vitamin D increases calcium absorption through the gut, that calcium and phosphorus will then be absorbed and that calcium and phosphorus fecal excretion will be reduced.

In order therefore as they progressively occur the effects of vitamin D may be listed as follows:

- 1 Increased calcium and phosphorus absorption through the gut
- 2 Decreased fecal calcium and phosphorus excretion.
- 3 Increased serum calcium.
- 4 Decreased parathyroid function as a result of rise of serum calcium. With decreased parathyroid function serum phosphorus will rise because the renal tubules reabsorb more phosphorus.

5 As vitamin D is increased to toxic levels the effect upon calcium is enhanced so that increase in urinary calcium excretion occurs. This will continue if vitamin D effect is great enough until more calcium is lost from the urine than is saved by decreased fecal excretion. Therefore the patient will go into negative calcium balance. In such instances the urinary phosphorus excretion rises more than the fecal phosphorus excretion falls. Therefore the serum phosphorus level will fall. So Albright postulates

that large doses of vitamin D will affect phosphorus metabolism much like parathyroid hormone. He does this by the observation that serum phosphorus falls and urinary phosphorus increases on high vitamin-D intake in parathyroidless individuals.

These cases have no parathyroids to be depressed by an elevated serum calcium from increased calcium absorption from the gut.

This has led to an interesting correlation of the action of vitamin D, dihydrotachysterol (A.T. 10) and parathyroid hormone on calcium absorption via the gut and urinary phosphorus excretion. This is summarized in Albright's table⁴:

	Calcium Absorption	Urinary Phosphorus Excretion
Vitamin D	++++	++
A.T. 10	++	+++
Parathyroid hormone	+	++++

It is interesting that A.T. 10 which is an intermediate irradiation product of ergosterol has an action between that of vitamin D and parathyroid hormone. It has been used therapeutically therefore to raise the blood calcium and to increase phosphorus urinary excretion in parathyroid tetany.

Thus when vitamin D increases absorption of calcium and phosphorus thereby making these available for calcification of osteoid calcification of the skeleton will proceed as an end-effect of this vitamin.

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Kidney Function as Related to Bone

We are interested in the kidneys primarily from the viewpoint of their relationship to phosphorus and calcium for obviously what happens to phosphorus and calcium will affect bone

The kidneys affect phosphorus and calcium by the mechanism of glomerular filtration and tubular reabsorption. Normal glomeruli filter the blood plasma of non-protein bound electrolytes. Protein-bound electrolytes are such large molecules that they cannot filter through the glomeruli. The glomerular filtrate will maintain the same concentration as the diffusible serum calcium and the inorganic serum phosphorus which is all diffusible^{1, 2} (Fig 13)

Large amounts of phosphorus and calcium filter through the glomeruli. Normally they are not lost to the body because the tubules reabsorb them. Tubular reabsorption of phosphorus and calcium is regulated by parathyroid hormones³ (Fig 16)

Tubular reabsorption of phosphorus is decreased by parathyroid hormone. It is triggered by an elevation of serum phosphorus. Conversely lowered serum-diffusible calcium induces an increase in parathyroid

secretion. This increases tubular reabsorption of calcium

It also appears that the hyperphosphatemic or hypocalcemic stimulating effects may occur simultaneously or separately. It is this latter that leads some to consider that parathyroid hormone has two active fractions.⁴

As far as concerns phosphorus and calcium the concentration in the glomerular filtrate is the same as in the serum. These are not threshold substances like glucose. Theoretically if no endocrine activity is present the tubular reabsorption of phosphorus will equal the glomerular filtrate and no phosphorus will appear in the urine (Fig 16 Sec. C I). Under these circumstances, the total glomerular filtrate of calcium would appear in the urine (Fig 16 Sec. D)

Conversely if maximum parathyroid activity is present none of the glomerular filtered phosphorus will be reabsorbed by the tubules and all of the filtered phosphorus will appear in the urine (Fig 16 Section C, III and IV). The calcium will be reabsorbed and its excretion in the urine will be reduced (Fig 16 Section D III)

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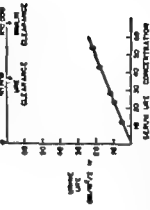
Fig. 16. Simplified diagrams of renal tubule reabsorption mechanisms and of the influence of endocrine factors upon them. The left hand group of schematic diagrams are constructed to show a blood vessel from which capes into a glomerular filter (glomerulus). The material (black dots) enters the renal tubule (lumen) then passes down the renal tubule (lumen) from which variable amounts are reabsorbed. The residue (white) passes down into a vessel at the bottom of the system. The number of dots in the various parts of the system represents the concentration or quantity of the substance in question. GF, glomerular filtrate; TR, tubular reabsorbate; TM, tubular maximal reabsorptive capacity; U, urine content; TS, tubular secretion.

In the schematic diagrams, units of quantities of material have been indicated by arbitrarily chosen small numbers. The graphs at the right of the schematic diagrams represent certain of the relations shown in the diagrams. However the

Section A - THRESHOLD MECHANISM (Glucose)



Section B - FRACTIONAL REABSORPTION MECHANISM (Urea)



Section C - ENDOCRINE MODIFIED FRACTIONAL REABSORPTION MECHANISM (Phosphorus)

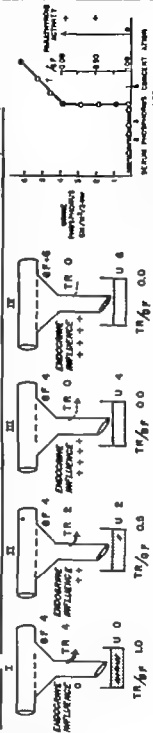


Fig. 16 PART 1 (Part 2 and remainder of caption on pp. 86 and 87)

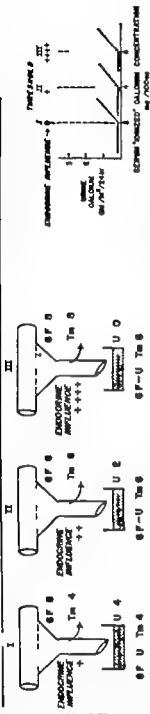
values assigned to the coordinates of these graphs are in Section A Threshold Mechanism. The schematic diagrams illustrate the effect of (Continued on next page)

FIG 16 (Continued)

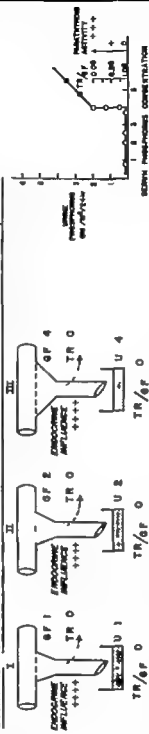
changing serum glucose concentration on the glomerular filtration, the tubular reabsorption and the urinary excretion of glucose. Note that the urine is sugar free until the amount of filtered glucose exceeds glucose T_m (threshold). At higher serum glucose concentrations, urine glucose content increases in proportion to the increase in serum glucose concentration. The graph at the right indicates that the serum glucose concentration equivalent of T_m is approximately 180 mg per cent.

Section B Fractional Reabsorption Mechanism
The schematic diagrams show the effect of changing serum urea concentration on the glomerular filtration tubular reabsorption and urinary excretion of urea. Note that in this instance tubular reabsorption removes a constant fraction of filtered urea ($TR/GF =$ approximately 0.5). There is no maximal tubular reabsorptive capacity. The urine contains urea at both high and low serum

Section D - ENDOCRINE MODIFIED "THRESHOLD" REABSORPTION MECHANISM (Calcium)



Section E - EFFECT OF CHANGE IN GLOMERULAR FILTRATION RATE (Phosphorus)



Section F - EFFECT OF TUBULAR SECRETION (Potassium)

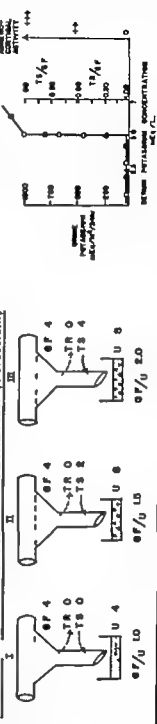


FIG 16 PART 2

urea concentrations, the amount being a constant fraction of the quantity filtered. The graph above indicates the

direct relationship between serum urea concentration and urinary urea excretion
(Continued on next page)

at the top of the graph the horizontal scale shows the relation of urea clearance to inulin clearance or glomerular filtration rate. Note that approximately half the urea in 100,000 cc of glomerular filtrate is "leaked" and appears in the urine ($U/GP \approx \text{approx. } 0.5$).

SECTION C. Endocrine Modified Fractional Reabsorption Mechanism
 This section shows the effect of an endocrine influence (parathyroid hormone) on the renal excretion of phosphorus. It is shown that, in instances I, II, and III, a constant serum phosphorus concentration is maintained. The effect of increasing endocrine influence is reduction of the action of filtered phosphorus reabsorbed by the tubules. When the endocrine influence is absent (instance I), essentially all the filtered phosphorus is reabsorbed ($TR/GP = 1$). Moderate endocrine influence acts in reabsorption of half the filtered phosphorus ($TR/GP = 0.5$). A maximal endocrine influence reduces the amount of phosphorus reabsorbed relative to the amount of phosphorus filtered essentially to zero ($TR/GP = 0$). Thus increasing endocrine activity provides for nearly excretion of increasing amounts of phosphorus without change in serum phosphorus concentration. On the other hand it is evident by comparison of instances III and IV that at a constant level of endocrine influence urine phosphorus excretion varies in direct proportion to urine phosphorus concentration (compare mechanism of Section B). A graph illustrates these relations again. The homeostatic sensitivity of the parathyroid gland appears to be the maintenance of constancy of serum phosphorus concentration. Hence endocrine influence is located as absent at serum phosphorus concentrations below average normal values. When serum phosphorus concentration rises to the average normal value of 4 mg. per cent, endocrine influence is shown to increase in proportion to needs for phosphorus elimination. This permits excretion of phosphorus to rise from negligible quantities to 4 Gm. 100 lbs. of body weight per 24 hours without a change in serum phosphorus concentration. The range through which urine phosphorus excretion varies as a result of changes in parathyroid influence is seen as limited at the upper end of the scale by the rate of glomerular filtration (see also Section E). At this point endocrine influence can do no further increase in urinary phosphorus excretion. Renal phosphorus excretion however may increase if filtration of phosphorus is permitted by an elevation of serum phosphorus concentration. Such rises in urinary phosphorus excretion will be proportional to increases in serum phosphorus concentration (see Section B).

SECTION D. Endocrine Modified "Threshold" Reabsorption Mechanism
 In contrast with its inhibitory effect on tubular phosphorus reabsorption, increasing parathyroid influence acts to augment tubular

calcium reabsorption. Furthermore renal excretion of calcium at a constant level of endocrine influence depends upon filtration of sufficient calcium to surpass the maximal reabsorptive capacity of the tubules (see "Threshold" mechanism, Section A). When the amount of calcium is less than Tm the urine is nearly calcium-free. When the amount exceeds Tm the excess calcium spills quantitatively into the urine. In the three instances shown by the schematic diagrams serum filterable or ionized calcium concentration is shown constant. In all instances sufficient glomerular filtrate calcium is indicated to saturate the tubular reabsorptive capacity. In instance I the tubular reabsorptive capacity is low as a result of minimal endocrine influence. Filtered calcium markedly exceeds the reabsorptive capacity of the tubules and large quantities spill into the urine. In instance II endocrine influence has increased the tubular reabsorptive capacity and a smaller quantity of calcium appears in the urine. In instance III where endocrine influence has caused an increase in tubular reabsorptive capacity sufficient to permit total reabsorption of the filtered calcium there is no spill-over into the urine. These relations are illustrated again in the graph at the right of the schematic diagrams. Here the effect of the endocrine influence on the serum calcium equivalent of Tm or threshold is to be contrasted with the graph of similar relations for glucose in Section A.

SECTION F. Effect of Change in Glomerular Filtration Rate
 This section shows the effect of changes in glomerular filtration rate on the upper limit of urinary excretion of phosphorus at a constant normal serum phosphorus concentration. Note that endocrine influence is represented as maximal in all the instances illustrated by the schematic diagrams. Under these circumstances urinary phosphorus excretion is directly dependent upon the rate of glomerular phosphorus filtration. In the graph at the right, glomerular filtration rate is shown as half that indicated in Section C. Note that, in comparison with the graph in Section C the range through which urine phosphorus excretion may vary without change in serum phosphorus concentration is reduced by 50%. With this exception the graphs of Sec. C & E are nearly identical.

SECTION F. Effect of Tubular Secretion
 The three schematic diagrams illustrate the way in which urinary excretion of a substance like potassium may be increased by tubular secretion. Such a mechanism augments the range of urinary excretion without change in serum concentration provided by the variable tubular reabsorption mechanism shown in Section C. The range is indicated in the graph at the right. (From Talbot Sobel, McArthur and Crawford, *Functional Endocrinology from Birth Through Adolescence*, pp. 56-59, Cambridge Mass. Harvard Univ. Press [for Commonwealth Fund] 1932.)

PART TWO

Living Bone in Disease

Developmental Faults

OSTEOGENESIS IMPERFECTA

(See Arolik's disease; idiopathic osteoporosis; Lobstein's disease; osteoporosis congenita; malacia myeloplastica; osteitis parenchymatosa chronica; dys-trophia periostalis; periosteal dysplasia; fetal rickets; annular rickets; fragilitas ossium (Klebs and Hochsinger); brittle bones; blue sclerae and otosclerosis (Ed-dowes or van der Hoeve's syndrome); osteoporosis periosteal dyscrasia; chronic parenchymatous osteitis (Schmidt); periosteal aplasia (Klebs); myeloplastic bone aplasia (Kardamatis); osteomalacia congenita (Jürgens); Durante's disease.)

Definition. Osteogenesis imperfecta is the term presently accepted for a rare disease starting in early or even embryonic life characterized by deficient matrix formation and abnormal fragility of bones. One form previously referred to as fragilitas ossium is familial and is characterized by blue sclerae and abnormally relaxed ligaments with a tendency toward dislocation and frequently is associated with deafness.

The larger number of cases are not familial. Clinically all of the cases may be considered as parts of one syndrome. For simplification a listing of the salient findings in this broad group is as follows:

- 1 Brittle bones with pathologic fractures
- 2 Relaxed ligaments and tendencies for dislocation
- 3 Blue sclerae in some cases
- 4 Otosclerosis in some cases
- 5 Osteoporosis and dwarfism due to deformity after fractures

In the literature appear many descriptions of cases that obviously are a part of this group. There has been much discussion

about those cases observed at birth, obviously beginning in intra uterine life and those cases starting postnatally.

Actually these cases are in general all alike. It simply appears that the earlier the case becomes manifest the more severe is the mesenchymal defect. Therefore the prenatal cases are more serious than the postnatal ones. Often they are stillborn.

It frequently has been observed that these cases spontaneously regress with puberty. Much speculation has resulted about this. The probable explanation is either the importance of estrogens in bone-matrix formation or simply the fact that most of growth has occurred by then and there is adequate bone for function, without rapid growth. On rare occasions the disease has been reported as occurring in sets of twins, concordant and discordant.

Historical Notes. There is no mention of bone fragility by either Hippocrates or Galen. According to Dry² Armand and France (1716) were the first to diagnose the condition of a patient with osteogenesis imperfecta. By the middle of the eighteenth century about 30 such cases had been reported. So early as 1788 O. J. Ekman³ submitted a thesis to the faculty of the University of Upsala on the subject of osteomalacia. He described the occurrence of multiple fractures and bodily deformity in a family including two brothers, a son of one of the brothers and two grandchildren.

Lobstein (1825) described the condition as a disturbance of osseous formation characterized mainly by fragility of bone. In 1833 he termed the condition "osteopathy, rosis" (Lobstein's syndrome today is termed osteogenesis imperfecta tarda in contradistinction to the syndrome described by Aro-



FIG. 17 *Osteogenesis imperfecta*, fetal type. Stillborn. Note fractures with healing and resultant deformities. The shafts of the long bones are widened and osteoporotic.

lik. The latter condition at present is referred to as the early or congenital form. However, it is the authors' opinion that even the delayed form is the result of a basic mesodermal defect which also probably has its origin in embryonic life.)

Gescheidt⁴ was among the first to describe the disease. Vrolik¹ named the disease *osteogenesis imperfecta*. Henschel⁵ described the occurrence of blue sclerotics. Cornaz⁶ noted the association between the fragility of bone and the presence of blue sclerae.

Spurway⁷ first called attention to blue sclerotics associated with fragility of bones in *osteogenesis imperfecta*. Eddowes⁸ observed the dual occurrence of abnormal blueness of the sclerae and brittle bones. He wrote

The transparency of the sclerotics indicates a want of the quality or quantity of the fibrous tissue forming the framework of the various organs of the body and probably explains the want of spring or toughness in the bones of these peculiar individuals.

Klenbock⁹ wrote that the condition was of endocrine origin. Deafness as a feature of the syndrome was described by Adair Dighton.¹⁰ In 1916 de Kleyn¹¹ was able to point out that a variety of deafness similar



FIG. 18 *Osteogenesis imperfecta*, infantile type. The skull shows mosaic of the wormian bones. The limb bones are widened, osteoporotic and deformed as a result of pathological fractures.

to osteosclerosis was found frequently in association with the other two conditions. Bronson¹² and van der Hoeve and de Kleyn¹³ added further data on deafness to the syndrome. Bauer¹⁴ and Weber¹⁵ stressed the congenital factors in the development of mesenchymal tissue. Key¹⁶ referred to the syndrome as "hereditary hypoplasia of the mesenchyme" and called attention to the hypotonicity of ligaments with hypermobile joints.

Incidence. The disease affects both sexes equally. The most common age¹⁷ for fractures is the preschool age up to the seventh year. There are few examples up to the fifteenth year. They are uncommon in adult life but beyond middle age they again become more frequent.

In the familial form the disease appears

to be transmitted through both males and females provided that one of the parents possesses the characteristics.

Bickel, Ghormley and Camp¹⁸ studied 40 patients with osteogenesis imperfecta. 11 of these were of the hereditary variety. In one patient the disease was traceable through 4 generations, all the afflicted members of which showed brittle bones, blue sclerae and deafness. (The average age was 15.2 years—21 males and 19 females. All 40 patients suffered from subperiosteal fractures caused by insignificant trauma.)

Blue sclerae are present in 90 to 100 per cent of persons afflicted.

Etiology. The cause is unknown. It appears to be a mesenchymal defect and the familial form has a dominant mendelian factor.¹⁷ Many of the infants are stillborn.



FIG. 19. Osteogenesis Imperfecta tarda type. White female 15 years old. (Figs. 19 to 22, service of Dr. A. Bruce Gill.) Normal blood chemistries. Balance studies on calcium, phosphorus and magnesium normal. Further studies after administration of thymus extract, Rountree type revealed no biochemical changes or clinical effect. Lateral view of skull. Changes are only those of osteoporosis and thinning of the inner and the outer tables. There are no deformities.



FIG 20 (*Top left*) Osteogenesis imperfecta, tarda type (Same patient as Fig 19) Rib cage spine pelvis. Anteroposterior view. The delicate thin configuration of the ribs and the clavicles is demonstrated. Similar changes are seen in the humeri the vertebrae and the pelvis.

FIG 21 (*Top right*) Osteogenesis imperfecta, tarda type. (Same patient as Fig 19) Lower extremities. Anteroposterior view. The extremely thin shafts of the long bones are bowed and osteoporotic. Pelvic deformity especially involving the acetabula, is present. These deformities are the result of simple bending of the porotic bone as well as pathologic fractures. There is considerable metaphyseal flaring at the knee.



FIG 22 (*Bottom*) Osteogenesis imperfecta, tarda type (Same patient as Fig 19) Left leg Anteroposterior and lateral views. Characteristic fragile bone structure is present with very thin cortical structure in the tibia the fibula and the tarsal bones. Note the obliquity of the proximal tibial epiphyseal plate.



FIG. 23 Osteogenesis imperfecta, tarda type. White male, 50 years old, who has survived despite frequent pathologic fractures associated with his condition. Anteroposterior view of skull. The suture lines are still open, late in life. The characteristic triangular shape is shown suggestively with bilateral bulging in the temporal regions. The tables are very thin.



FIG. 24 Osteogenesis imperfecta, tarda type. (Same patient as Fig. 23.) Lateral view of skull. The extremely delicate structure of the diploë and the inner and the outer tables is seen, giving the effect of a marked osteoporosis without any ground-glass appearance as is seen in hyperparathyroidism. The open suture lines are striking.

owing to damage to the unprotected brain during childbirth, the skull often consisting of a membranous bag with a few isolated plates of bone.

Varieties. The varieties of osteogenesis imperfecta may be grouped as follows: (a) fetal (b) infantile and (c) tarda.

FETAL. In the fetal variety the changes occur during development *in utero* and prevalently result in death before birth. The extremities are deformed owing to unhealed fractures (Figs 17 and 18). There are indications of delayed ossification in the skull and the face. The bones of the extremities are usually thickened and deformed but



FIG. 25 Osteogenesis imperfecta, tarda type. (Same patient as Fig. 23.) Pelvis and upper femora. Anteroposterior view. There have been bilateral multiple subtrochanteric femoral fractures with malunion and considerable excess callus formation. Osteoporosis is only of mild degree.

become long thin and fragile if the case survives more than a few months. The cortex is thinned and somewhat cancellous. The marrow is either fatty, gelatinous or fibrous. Many of these infants are stillborn because of damage to the unprotected brain during childbirth. The skull here is practically a "membranous bag of bones."¹⁸

INFANTILE. This form is less severe than the infantile form (Figs 19 to 28). The cases survive even to adult life although this is rare. These cases sustain many fractures and resultant deformities. The cranium ossifies better than the fetal variety but the ossification does not become complete.

TARDA. This type is still more benign than the infantile form (Figs 19 to 28). The child may appear to be normal at birth. During childhood fractures occur from relatively small trauma. This often is the first sign of the disease. When adolescence is reached the susceptibility to fractures is reduced. Many thoughts to explain this phenomenon have been advanced. Gonadal function may play a part in stimulation of matrix formation. The fact that rigid growth is reduced and stimulus from stress continues may also contribute to the remission.

This last group of cases is often of the familial type with blue sclerae, deafness of otosclerotic type and ligament relaxation.

Clinical Features: PHYSICAL—SIGNS AND SYMPTOMS. The prenatal type are usually stillborn or die soon after birth. In the milder or delayed forms the occurrence of frequent fractures may be the major indication of abnormality.

Signs and symptoms are confined entirely to the bones which are extremely fragile. The subsequent deformities are due to the fractures which unite normally and painlessly although frequently in severe malposition. The callus formation is normal and at times may be excessive. This may give the bones an irregular beaded character observable in the roentgenograms. Furthermore, bending or bowing of involved bones appears without single demonstrable frac-

ture to explain it. This probably is due to numerous successive small fractures.

Except in very mild forms the patients are dwarfed, deformed or both. This is in part attributable to deformity from malunion of fractures, also probably to retardation of growth at the epiphyseal lines. The deformities are greater in the extremities than in the trunk. (The formation of cartilage and its calcification proceeds normally.)

In the severe infantile variety the peculiar shape of the skull is characteristic. It resembles an inverted triangle with the base of the triangle representing the top of the skull. The forehead is broad and bulges forward and the parietal bones bulge over the external auditory meati pushing the ears downward and outward. The thoracic cage appears deformed. Palpation reveals evidence of nubbins on the ribs or the long bones. Owing to fresh fractures there may be crepitus and preternatural mobility in the extremities, the clavicles or the ribs. The infants readily succumb to intercurrent infection.

Physical development is extremely slow with intellectual development not affected appreciably. The deciduous teeth appear rather translucent because of poor calcification. The permanent teeth appear to be more normal, however there is a gradual narrowing of the pulp areas and the canals.²⁰ The musculature is extremely feeble in all but the milder examples. The hypotonicity is of course related to fractures and deformities and long-standing disuse.

Deafness appears only after the brittleness subsides. It is rarely present until after 20 years of age. Improvement as concerns reduction of the incidence of fractures progresses with increasing age.

CHEMICAL AND METABOLIC DATA. The ash content of the bone is low—sometimes as low as 24 per cent (Normal 60 per cent.) Repeated analyses for serum calcium and inorganic phosphorus fail to show any material changes. The alkaline phosphatase activity of the plasma falls clearly in the normal range.



FIG 26 (*Top left*) Osteogenesis imperfecta, tarda type (Same patient as Fig. 23) Both legs. Anteroposterior view. Note the slender cortical bone structure with metaphyseal flaring at the upper tibiae. On the right side the healed fracture of the leg bones can be seen, with residual lateral bowing.



FIG 27 (*Top right*) Osteogenesis imperfecta, tarda type (Same patient as Fig. 23) Both legs. Lateral view. The deformity of the right leg can be seen to be an anterior as well as a lateral bow with resultant shortening. A milder fracture of the left tibia has healed without deformity.

FIG 28 (*Bottom*) Osteogenesis imperfecta, tarda type (Same patient as Fig. 23) Both feet. Anteroposterior view. Deformities of the various metatarsal shafts have resulted from malunion of multiple fractures. The cortical bone structure is somewhat thin.



Inadequate retention of calcium and phosphorus occurs—the retention is about one third to one half that of normal children. However repeated balance studies done by the authors have demonstrated no negative balance. The reason for the inadequate retention therefore is the fact that there is not so much skeleton to calcify as in a normal person.

There is a high thrombocytic count—about 500,000.

Delcourt²² always found the sedimentation rate increased in osteogenesis imperfecta but this has not been the authors' experience. The bone marrow findings were characterized by moderate plasmocytosis and hyperplasia of the red marrow.

ROENTGENOGRAPHIC DIAGNOSIS *General Considerations* The roentgenographic features obviously differ according to the variety of the disease.²³ To be noted are (1) osteoporosis (2) great thinning of the cortex (3) diminution in thickness of the shaft in the middle with some flaring toward the diaphysis (4) coarse trabeculations (5) normal epiphyseal metaphyseal relationships and (6) multiple fractures.

Prenatal Variety The most common pronounced feature is multiple fractures in osteoporotic bone (Figs. 17 and 18). Most characteristic are the various stages of callus formation especially in the ribs.

In the young infant the skull is composed of islands of ossification forming a mosaic of wormian bones (Fig. 18). Distortion of the skull owing to posture effects is seen later.

The separate long bones tend to be slender with thinning of the cortex and apparent widening of the marrow space in spite of the slender appearance (Figs. 20 to 22, 26 and 27). The cortex may be so thin that the periosteum seems incomplete.

The extreme decalcification is diffuse and the trabeculation is rather fine.

X-ray pictures show that outlines of the vertebral bodies are defined clearly. They are little more than half the depth of the normal bodies and show slight indentation

in the midline on both the superior and the inferior aspects and biconcavity similar to the codfish tail vertebra of Albright in osteoporosis. The laminae are closely approximated in the dorsolumbar area, but above and below this there is an ever widening gap between them.

Bornebusch²⁰ studied the vertebrae of some patients with Lobstein's disease. He found that in children the size of the osseous nuclei of the vertebrae commonly appears normal. The width of the spinal canal is unaffected, however trabeculae are thin and small. He found kyphosis and scoliosis to occur as a result of compression of the fragile osseous tissue. Other deformities of the vertebrae, such as flattening are sometimes present.

The clavicles give a ribbon effect. The scapulae are irregular and usually creased. The ribs are also creased with a ribbon effect (Fig. 20). The humeri are shorter and thicker than normal, creased, irregular and granular; there is retarded epiphyseal ossification. The appearance of the radii and the ulnae is similar to that of the humeri.

(The lower ends of the radii and the ulnae are affected notably in persons with generalized disturbance of skeletal growth. The ulna usually is affected more than the radius particularly in the direction of reduction in length. The fibula is much less involved.)

The metacarpals and the phalanges are similar to other long bones but less defined. The pelvis is irregular and greatly decreased dimensionally. The femora are short, stumpy, creased, devoid of all normal features; the lower epiphysis is visible. The tibiae and the fibulae are short, stumpy and irregular. The metatarsals and the phalanges are similar to corresponding bones of the hands.

The same roentgenographic findings that are seen in the more severe prenatal type are to be observed in the tarda variety (Figs. 19 to 28). Obviously this latter variety is much less severe than the former. Therefore the degree of deformity will be less marked

and the development of the osseous skeleton will be better and a more normal type. Fractures and deformities of course do occur.

Three interesting phases of osteogenesis imperfecta have been added to the group that the authors usually observe and it is of interest to refer to Fairbank and others for descriptions of the "thick bone variety" (Fig. 17) the "hyperplastic callus" group²² and a form that is predominantly cystic in type²³ in which there is pronounced honeycombing of bone.

Pathology. The essential pathology is defective formation and defective calcification of bone trabeculae. The bone is discontinuous and fragmentary.²⁴

GROSS APPEARANCE. Flexibility, brittleness and deformity are present as the characteristic features of the osteoporotic bones which are soft. Changes in the long bones are pronounced. In separate bones there is great variation in the appearance from thin shafts with normal curvature to severe deformities with fractures and callus formation (Figs. 17, 18, 21, 22, 25 to 28).

On cut section the shaft appears slender and the cortex extremely thin and in advanced stages even of eggshell thinness. The periosteum is irregular and sometimes appears incomplete. The epiphyseal and the metaphyseal relationships are normal but may be impaired by deformities of the softened bones (Figs. 21 and 22). The diaphyseal ends are flared and appear relatively enlarged. There may be extreme angulations (Figs. 21 and 25). In severe conditions pseudointerphalyses may be seen where stress and strain and continuous movement have interfered with fracture healing.

The skull is bizarre in appearance and on palpation (Figs. 23 and 24). The centers of ossification tend to remain separated producing a mosaic pattern made by many separate islands of small bones (Fig. 18). Single vertebral bodies also may be flattened and thinned with consequent expansion of the intervertebral disks.

Microscopic Appearance. To get a picture of this process one must visualize endo-

chondral bone formation in its microscopic form. Normally, cartilage columns appear at the metaphyseal side of the epiphyseal plate. They calcify. Then capillary loops come in bearing osteoblasts and a break up of the calcified cartilage with reformation into bone occurs. In this condition a defect in the osteoblast cycle appears to be present. The absorption of calcified cartilage with conversion into bone occurs not in a uniform and normal manner but in a spotty haphazard fashion.

So as an end-picture we see a deficiency of metaphyseal and therefore eventually of diaphyseal bone trabeculae. Cartilage islands remain marooned and appear to change in places into bone by direct metaplasia.

In addition to the metaphyseal defect there is a deficiency of osteoblasts in the periosteum. The fibrous layer of the structure is thickened and the cambium layer is largely acellular, thinned and irregular.

Diagnosis. The diagnosis of the prenatal type is usually easy. No other syndrome in the newborn is observed with numerous fractures and characteristic roentgenographic appearance. There may be blue sclerae and family history and joint laxity in addition. These latter are not necessary for the diagnosis however.

Differential Diagnosis. In general it is best to bear in mind that the following conditions lead to fragility of bones: (1) all forms of rickets and osteomalacia, (2) scurvy, (3) hyperparathyroidism, (4) Paget's disease and (5) osteoporosis.

Achondroplasia may present superficial resemblance to osteogenesis imperfecta. The differentiation is made by radiographic examination which will show thick strong bones with a normal trunk (Figs. 73 to 76).

The congenital variety of osteogenesis imperfecta may be confused with syphilis. Sometimes differentiation must be made from hyperparathyroidism (Figs. 117 to 133). In osteogenesis imperfecta, the blood calcium, phosphorus and alkaline phosphatase are normal while in osteitis fibrosa

cystica, the blood calcium is elevated the phosphorus is depressed and the alkaline phosphatase is usually increased

Complications. Various lesions of the skeleton are sometimes concurrent. Thus Bromer²² reported a case of osteogenesis imperfecta in a 3 month-old infant with rickets and scurvy Brailsford²³ referred to a complication which he described as a condition suggesting scurvy, in which subperiosteal hemorrhages were more predominant than fractures

Treatment. There is no specific medical treatment. The patient should be protected against injury and fractures. Whenever fracture occurs the fracture may be expected to heal well and early. Proper measures to reduce the fracture and hold it in good position to obviate deformity are indicated.

On theoretical grounds judicious use of estrogen with small doses of androgen is indicated. Vitamin D and a high calcium phosphorus and protein diet would also appear to be of value. Effort to keep the child active to stimulate bone formation should also be made. This in turn will improve muscle tone.

Prognosis. In the prenatal group the infants are usually stillborn or die early. In the tarda variety there may be great variation in severity of involvement which would infer a difference in prognosis. The more severely affected children ultimately are greatly deformed.

FIBROUS DYSPLASIA OF BONE

POLYOSTOTIC FIBROUS DYSPLASIA

(Syn. Albright's syndrome; polyostotic fibrous dysplasia; polyostotic osteitis fibrosa; osteodystrophia fibrosa; fibrocystic disease of bone; regional fibrocystic disease—Pheaster; osteofibrosis deformans juvenilis fibrosa unilateralis; polyostotic skeletal cystofibromatosis and osteitis fibrosa with cartilage formation; osteitis fibrosa disseminata; unilateral fibrosa cystica generalisata.)

Definition. Fibrous dysplasia of bone is

a disease of bone characterized by regressive changes—thinning of the cortex and replacement of the marrow by fibrous tissue containing abnormal fibrous bony spicules.

Polyostotic fibrous dysplasia (Jaffe Lich tenstein)^{1, 2} consists mainly of interference with skeletal development. There is excessive replacement of bone marrow by dense fibrous connective tissue. The most frequent sites of involvement are the diaphyses and the metaphyses of the long bones and the adjacent parts of the shoulder and the pelvic girdles. The association of lesions in bone, skin and endocrines is usually termed Albright's syndrome.³ There is now wide acceptance of the term fibrous dysplasia of bone. When there are also nonskeletal manifestations the term Albright's syndrome is widely used. The term osteitis fibrosa disseminata is used to differentiate the condition from osteitis fibrosa generalisata (hyperparathyroidism) and osteitis fibrosa localisata (unicameral bone cyst).

Historical Notes. Bone disorders of a fibrocystic nature have long been known. Obviously, in light of present knowledge, it is easy to understand the confusion that existed before careful clinical, roentgenologic and laboratory work was carried out.

First to describe this disease group in detail was von Recklinghausen⁴ although even he appeared to be confused with regard to at least two of his cases. These two were examples of fibrous dysplasia and not of osteitis fibrosa generalisata.

This confusion of course continued until the classic work of Mandl⁵ in 1926 when the etiology of osteitis fibrosa generalisata was correlated with a parathyroid adenoma. From then on the separation of this form of cystic disease was assured. Furthermore, reports predating Mandl now clearly indicate the observation of fibrous dysplasia.

The first report of what apparently was an example of fibrous dysplasia of bone was by Wieland.⁶ Well⁷ first described the syndrome of precocious puberty, fibrocystic bone disease and pigmentation of the skin. Von Recklinghausen listed a number of un-

related diseases which had as a common characteristic the presence of fibrocystic like bone changes. Some of those he described may have been in the category of polyostotic fibrous dysplasia. In England⁸ Telford reported one case of osteitis fibrosa with formation of hyaline cartilage which was probably an example of fibrous dysplasia of bone.

Golkammer⁹ recognized a disease which he characterized as osteodystrophia fibrosa unilateralis with pubertas praecox. In the same year, Borak and Doll¹⁰ described what they called unilateral Recklinghausen's disease of bone with pubertas praecox.

In 1937 Albright et al¹ described the curious clinical syndrome characterized by (a) bone lesions which have a notable tendency to be unilateral and which show osteitis fibrosa on histologic examination (b) brown nonelevated pigmented areas of the skin, which tend to be on the same side as the bone lesions, and (c) an endocrine dysfunction which in females is associated with precocious puberty.

Lichtenstein and Jaffe¹² coined the term polyostotic fibrous dysplasia. They endeavored to show that in all examples of the disease the nucleus of the disorder appeared to localize in the bony lesions which when widespread were associated at times with one or more of the other manifestations of Albright's syndrome. They wrote:

The name polyostotic fibrous dysplasia is being used to designate a skeletal developmental anomaly affecting several or many bones with predominantly unilateral involvement. The involved bones show filling of their medullary centers by gritty grayish-white fibrous tissue containing trabeculae of newly formed primitive bone.

Incidence. Fibrous dysplasia of bone is an uncommon disorder. It usually begins in childhood and ceases spontaneously after puberty. The disease is more common in the female than in the male.¹¹

Etiology. Many suggestions have been made as to the cause of polyostotic fibrous dysplasia but none has been accepted generally. In the past it was assumed that the disease was

1 An atypical variety of von Recklinghausen's neurofibromatosis

2 An uncommon class of xanthomatosis

3 A disease of the hypothalamic area of the brain

4 Disturbance in storage and utilization of vitamins in the liver resulting in a disturbance of bone growth.

5 Precocity caused by pressure on the hypothalamus secondary to overgrowth of the bone at the base of the skull

6 An unusual variety of Ollier's disease or multiple enchondromatosis.

7 Abnormality of bone-forming mesenchyme sometimes in association with other developmental defects. Stauffer et al¹³ reported a case with multiple arteriovenous fistulae

8 A primary neurologic defect

9 Intra-osseous hemorrhages in fibrous tissue in the bone marrow perhaps with secondary formation of cysts (Pommer)

The most reasonable suggestion to account for the disease is a developmental defect in bone-forming mesenchyme. A primary hormonal imbalance has been postulated in those examples in which sexual aberrations were especially distinguishable.

Varieties. In the main two forms of fibrous dysplasia of bone are now recognized—the diffuse or polyostotic and the monostotic. The diffuse is much more common.

In the polyostotic form the disease is a congenital anomaly usually with unilateral involvement of multiple bones. Bilateral disturbance does occur. The patient ordinarily comes under scrutiny in childhood or early adolescence.

Albright¹ and his associates have emphasized the extraskeletal features that may occur in this disease. Conversely Kurczok¹⁴ has described a case of extraskeletal findings with no bone changes. These extraskeletal manifestations include pigmentation of the skin and early sexual precocity. Later, there is premature closure of the epiphyses and endocrine dysfunction in the form of sexual precocity in females. "No consistent abnor-



FIG 29 Polyostotic fibrous dysplasia. Healed fracture of the mid-shaft of the left humerus with expansile involvement of most of the shaft



FIG 30 Polyostotic fibrous dysplasia. Tibia and fibula. Cystlike change of the lower tibia. Expansion and bowing of the mid tibia. Expansile cystlike area in the mid fibula.

malinity in gonadal function has been elicited in the male patients.¹³ Concurrent hyperthyroidism is occasionally recorded.¹⁴

Clinical Features: SIGNS AND SYMPTOMS
The onset is usually insidious. Attention may be directed to an involved bone by a variety of incidence such as fracture appearance of deformity owing either to bending or local enlargements of a bone or the development of asymmetry of the face and the skull. A common finding is pigmentation composed of small to large melanotic spots giving the typical "café au lait" appearance. These spots have irregular edges which differentiate them from the smooth edges of spots in neurofibromatosis.

According to Lichtenstein.²

This abnormality appears in childhood or in early adult life and evolves slowly pursuing a protracted clinical course characterized by pain deformity and by the tendency to pathologic fracture.

Progressive deformity and shortening of a limb may be seen subsequently. Rarely is an involved bone seen to be shorter than its counterpart. When there are changes in the face and the skull or in the jaw exophthalmos and even severe displacement of an eye may develop gradually.

Pain as a rule is not severe.

Usually before the age of 4 the disease has become apparent by the appearance of the aforesaid facial asymmetry or unilateral bowing with enlargement of one or more of the long bones. Precocious puberty is rarely the first sign. The bones more commonly affected are femur (Figs 31, 33, 37 to 39) pelvis (Figs 33 and 37) skull scapula



FIG 31 Polyostotic fibrous dysplasia. (Figs. 31-32 from Dr. M. M. Pomeranz) Marked involvement of the entire upper femur with deformity of the femoral head and neck.



FIG 32 Polyostotic fibrous dysplasia (Same patient as Fig. 31) Cystlike involvement of the left tibia.

and tibia (Figs. 30 and 32) humerus (Figs. 29, 35 and 36) metacarpals and metatarsals. In consequence there is disturbance of gait and often spontaneous fractures occur.

Mild varieties of the disease may be asymptomatic at first but are discoverable on roentgenographic examination for other causes. In girls in the Albright variety sexual maturation may start as early as the second year and cease in early childhood.

In the rare progressive condition with involvement of almost the entire skeleton there may be invalidism and incapacity during childhood or subsequently with fatal termination.

CHEMICAL DATA *Laboratory Data* Biopsy is necessary for final diagnosis.

The results of chemical analyses of blood, urine and feces are usually as follows: values for serum calcium and serum phosphorus are variable but ordinarily are within normal limits as are other constituents of the blood. Serum alkaline phosphatase occasionally is increased. Studies of calcium balance in the disease have varied but in general show normal values. High values for serum cholesterol have been reported and when so have resulted in the mistaken diagnosis of xanthoma of bone.

Albright reports premature secretion of FSH, pituitary follicle-stimulating hormone, moderately elevated BMR which ought to be checked by protein bound iodine and iodine uptake studies.

ROENTGENOGRAPHIC FEATURES The roentgenographic data are variable and are de-



FIG. 33 Polyostotic fibrous dysplasia. White female 16 years old. Involvement of the upper right femur and the pelvis.

"Café au lait" spots on the upper back. Chemical studies including serum calcium, phosphorus and alkaline phosphatase and urine calcium and phosphorus excretion were normal. The patient has had no specific treatment. She is now in her late 20's, is married and has had a normal pregnancy; does her own housework; has had no fractures.



FIG. 34 Polyostotic fibrous dysplasia. (From the service of Dr. A. Bruce Gill, followed and treated by the senior author.) White male 14 years old. Cystic lesions of numerous ribs and cystic lesion of left humerus, after unsuccessful bone-graft operation.

pendent upon the stage of the disease. The site of predilection appears to be the metaphysis of the long bones, although sometimes the lesion may appear in the middle of the shaft. It also has been found in all bones.

The roentgenologic manifestations are usually central (though sometimes periosteal) cystlike areas of translucency and as a rule contain coarse trabeculae (Figs. 32 and 38). In general the following features are present: (a) broadening or expansion of bone (Fig. 29); (b) thinning of the cortex (Figs. 30 and 31); (c) rarefied and apparently trabeculated and cystic appearance (Figs. 35 and 36) (cysts actually are radiolucent fibrous or uncalcified osteoid areas); and (d) secondary deformities (typical is shepherd's crook in the upper femur) (Figs. 33 and 39).

In polyostotic fibrous dysplasia, the entire skeleton (one half of it) or isolated bones of

any part of the osseous system may show proliferation of fibrous tissue within an ossified shell which reveals expansion compared with the adjacent normal bone. The expansions are regular, all cancellous structure having been absorbed. There is a density which is a little less than that of normal bone.

The solitary lesions most often cause difficulty in diagnosis. When there is extensive skeletal involvement, the lesions are often bilateral, most of the lesions being on one side. The lower extremities are involved more frequently than the upper ones. Normal bone is present between the areas of abnormal bone.

The flat bones—e.g., clavicle, ribs, pelvis and cranial vault—on roentgenographic examination show characteristic fibrocystic osseous change with variable severe tumes-



FIG. 35 Polyostotic fibrous dysplasia (Same patient as Fig. 34 now 16 years old.) Left humerus, 2 years later. Cystic lesions of the mid-shaft of the left humerus with further marked invasion and destruction of bone substance.



FIG. 36 Polyostotic fibrous dysplasia. (Same patient as Fig. 34 now 16 years old.) Left humerus 4 months later. Postoperative result following implantation of tibial bone grafts. At surgery some fluid and smooth cyst wall similar to unicameral cyst were observed.

cence and coarse loculation resembling a boneycomb.

Cystlike areas consist of fibrous-tissue deposits which cause replacement of the normal trabecular structure and give a homogeneous granular appearance devoid of bony architecture. As they enlarge they cause pressure on the surrounding cortical bone. If the area of involvement is nearer the medullary aspect this pressure is effective in the direction of least resistance—toward the medullary canal—forming a crescentic inner border. If less resistance is offered by the cortical layer, localized expansion is obviously outward. Extremely superficial lesions frequently induce rounded “blisters” on the surface of the bone.

As these rounded areas become larger they may encroach upon each other giving the appearance of pseudoexpansion. The bony outline may then assume a knobby appearance. Shell like thinning of the cortex may follow causing weakness of the bone and eventual spontaneous fractures.

No evidence of periosteal elevation is seen unless in consequence of fracture. Osteoporosis does not occur.

Pathology: Gross Appearance. The gross appearance of the lesion is that of a symmetric fusiform or almost spherical swelling ranging up to 6 cm. in diameter. The surface consists of thin but intact cortical bone. On longitudinal section the cancellous bone and marrow are replaced by a firm yellow white tissue containing occasional small cysts usually filled with amber fluid.

Widening and elongation of the bone oc-



FIG 37 Polyostotic fibrous dysplasia. (Same patient as Fig 34 14 years old) Multiple cystic lesions of both sides of the pelvis and bilaterally in the upper femora.



FIG 38 Polyostotic fibrous dysplasia. (Same patient as Fig 34 14 years old) Multiple cystlike lesions in both femora. Healed fractures in the mid shaft of the right femur

cur as a result of the hyperplastic process within the medullary canal and the interstitial spaces. The epiphyseal centers appear to be unaffected the end of the metaphysis and the epiphyseal cartilage may be involved.

The disease may involve both membranous and endochondral bone. The interior of the bone is replaced by grayish yellowish fibrous tissue which may reveal islands of cartilage calcification ossification or minute cyst formation. These cysts are usually the result of degeneration. Vascular areas occasionally are noted. The cortex is thin and the bone shaft may be increased in width. Bowing deformity of extremities is evident and in the femur the bowing is often so extreme as to produce the typical "shepherd's crook." Pathologic fractures are common.

In the Albright variety there are signs

and symptoms of precocious puberty in females. None is noted in males.² There are also pigmentation of skin café au lait spots and a marked tendency toward unilateral skeletal involvement.

The bone lesions are disseminated but appear to have a predilection for the occiput the metatarsals and the metacarpals the phalanges the upper end of the femora and the tibiae.

In 67 cases of monostotic bone lesions Schlumberger¹³ found the distribution to be as follows: ribs 29 femur 9 tibia 8 maxilla 7 calvarium 5 mandible 2 humerus 2 ulna 2 vertebra 1 pelvis 1 fibula 1. The small bones of the hands and the feet were not affected in this series of monostotic cases.

MICROSCOPIC APPEARANCE. Microscopically the outstanding feature is the proliferation of connective tissue which is composed of rather immature spindle cells

either loosely or tightly packed. The spindle shaped fibroblasts show a tendency to lay down osteoid tissue or bone by direct metaplasia. This bone is of an abnormal fiber type.

Trabeculae and cartilage island may vary in size and number. The cortex shows thinning from pressure of the internal expanding fibrous mass. Cystic areas observed on the roentgenogram are actually radiolucent areas of fibrous tissue or uncalcified osteoid.

Since immature uncalcified osteoid is difficult to reabsorb, the tendency for expansion and deformity of this mass continues.

Diagnosis. In general the diagnostic points to bear in mind are (a) early age (b) conspicuous bone deformity particularly of the skull and the long bones (c) predominantly unilateral skeletal involvement (d) pigmentation of the skin corresponding to the area of the bone lesion or lesions (e) precocious puberty in females (not observed in males) and (f) essentially normal biochemical data.

Differential Diagnosis. There are a number of affections of the skeletal system in which fibrosis forms a part of the pathologic changes.

It may be said in general that polyostotic fibrous dysplasia is easily differentiated from other varieties of bone involvement if the extraskletal lesions, abnormal skin pigmentation and sexual precocity in the female are present (See Table 8 p. 469).

HYPERPARATHYROIDISM. The first condition to be differentiated and cleared is hyperparathyroidism. The differentiation here can be done quite easily on the basis of blood chemistries and if necessary balance studies. The blood chemistries as indicated above in the discussion of polyostotic fibrotic dysplasia are relatively normal as is the urine. In hyperparathyroidism the urinary calcium excretion is high. Balance studies show a loss of calcium and phosphorus from the body. The serum calcium is elevated, the phosphorus is lowered. The alkaline phosphatase is uniformly elevated.

Biopsy of course proves again a differentiation because the histology of the two



FIG. 39 Polyostotic fibrous dysplasia. (Top) White female 20 years old. Typical shepherd's-crook deformity of the left upper femur. The right upper femur also is involved with expansile reaction. (Bottom) The photomicrograph shows partial reabsorption of bone and new formation of osteoid tissue. Hematoxylin-eosin. ($\times 36$) Photomicrograph prepared by Dr. William Ehrlich.



conditions is very definitely different. The characteristic pathologic finding in hyperparathyroidism is osteoclastic invasion of trabeculae. The phenomenon observed in the polyostotic fibrous dysplasia is fibrous tissue with bony metaplasia but no osteoclastic reaction.

PAGET'S DISEASE. Paget's disease of bone in certain instances also may show patterns similar to those seen at least roentgenologically in polyostotic fibrous dysplasia (Figs 290 to 291). Balance studies here in the osteoblastic phase will show a retention of phosphorus and calcium and a loss of sulfur. Chemical findings are uniformly an increase in sedimentation rate and a high alkaline phosphatase where the chemistries in polyostotic fibrous dysplasia are normal. The bone characteristics in Paget's disease are usually those of an osteolytic wedge formation which occurs as the primary factor of the disease. This is closely followed by an osteoblastic reaction. This, of course, results in a distortion of the gross bone structure. It has been described often as low-grade bone absorption, low-grade bone formation with scattered cysts and islands of hypercalcification. Despite severe changes in bone structure, the roentgen shadows and the anatomic form of cortical cancellous and medullary bone will remain apparent.

Wide trabeculations are common in Paget's disease. The cystic forms tend to be of a type different in appearance from that of the translucent type seen in polyostotic fibrous dysplasia. Rarely does the degree of deformity occur in Paget's disease that is observed in the polyostotic fibrous dysplasia, at least as concerns the thigh and hip area. Finally, of course, the age is a strong differentiating point.

Histologically, the appearance of Paget's is characterized by the mosaic bone structure which is of course quite different from that seen in polyostotic fibrous dysplasia.

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE). This is particularly difficult to differentiate from polyostotic fibrous

dysplasia, and at least one author Thannhauser, thinks that they are the same disease.¹⁴

It is well to recall that the following features are characteristic of multiple neurofibromatosis: (a) hereditary affection (b) "café au lait" pigmentation (c) sessile or pedunculated tumors on the skin (d) bone cysts at the ends of long bones—femur or upper end of tibia—may be bilateral sharply circumscribed areas of destruction with little, if any, evidence of bone formation (e) endocrine disturbance, e.g., hypoparathyroidism (f) mesenteric ganglioneuromas and (g) intracranial or spinal tumors.

Von Recklinghausen's neurofibromatosis with its characteristic pigmentation of the skin also may be associated with osseous lesions and thus complicate the problem of differential diagnosis. The presence of neurofibromas along the course of cutaneous nerves provides an important clue. The diagnosis can be settled by biopsy (Fig. 91). Neurofibromas do not occur in Albright's syndrome.

The basic cause of the bone changes is the development of a neurofibroma in one of the perosteal nerves. As the tumor enlarges, pressure is exerted on the bone cortex causing erosion and pit formation. These depressions are filled with neurofibromatous tissues. In the roentgenograms, they sometimes mimic cysts and at times a thin shell of cortex covers the fibrous tissue. Biopsies are of aid if nerve stains are done.

Whenever bone is involved in neurofibromatosis, it appears to be a direct invasion of bone by these nodules. The skeletal changes therefore are not so widespread as they are in polyostotic fibrous dysplasia.

In polyostotic fibrous dysplasia, the character of the pigmentation of the skin differs from that of neurofibromatosis. In the former (namely polyostotic fibrous dysplasia) the pigmentation is irregular about its edges and not so smooth as it is in neurofibromatosis.

OLLIER'S DISEASE. Multiple enchondromatosis may be considered to include the Ollier

variant which is sometimes alluded to as a dyschondroplasia. These cases are not usually associated with pigmentation changes in the skin. Although cystic areas may be observed in the metacarpals or the metatarsals a biopsy will show the differentiation with the elements representing primarily cartilaginous material (Figs. 53 and 54). Furthermore, in this phase of multiple enchondromatosis the spread into the long bones or in the flat bones does not tend to be so widespread as is observed in the polyostotic fibrous dysplasia and deformities are not so likely to occur (Figs. 55 to 59). This condition also is not commonly associated with fractures but is associated to very marked degree with involvement and disturbance of the epiphyses.

RETICULOENDOTHELIOSIS In particular Hand Schüller-Christian disease may also be confused with fibrous dysplasia. The most common sites are the skull and the pelvis whereas the long bones are seldom involved (Figs. 247 to 256). The bony defects are usually maplike. The disease usually occurs in early life.

Hand Schüller-Christian disease often is found as a triad: exophthalmos, geographic skull and diabetes insipidus. Pigmentation and sexual precocity are not found in lipoid disease.

The more recent consideration in regard to the etiology of this disease is that it is a granuloma with secondary lipoidification.

LIPOMATOSIS Caucher's and Niemann-Pick's diseases may bear a superficial resemblance in the radiographic appearances of the bones to polyostotic fibrous dysplasia but each of these diseases has sufficient other clinical characteristics apart from the histologic aspects of the bone biopsy to distinguish them readily (Figs. 257 to 261).

There is however what some have considered to be an atypical Hand Schüller-Christian disease namely xanthomatosis generalisata ossium in which involvement of the long bones and the joints occurs. The blood cholesterol may be elevated here. In these examples unless the diagnosis is sus-

pected the biopsy tissue may be so fixed that the storage cells cannot be seen or stained suitably.

HEMANGIOMAS OF BONE. In sites other than the vertebral bodies hemangiomas of bone may have certain features in common with polyostotic fibrous dysplasia. A biopsy will serve to differentiate the two conditions. The gross appearance of the two lesions is also entirely different.

SARCOMA Sarcoid bone lesions usually are limited to or are most notable in the hands (Figs. 322 to 326). The elevation of total plasma proteins frequently the reversal of albumin globulin ratio, the presence of a globulin in excess in the blood and the characteristic skin, lung and eye lesions differentiate the condition.

ADRENAL TUMORS Adrenal tumors may be recognized by the fact that those producing precocious puberty (cortical) rarely metastasize to bone and those metastasizing to bone (medullary) do not produce precocious puberty.

SYPHILIS In congenital syphilis the form that is most likely to be cystic is the osteomyelitic. The lesions usually are multiple. The changes usually are found in the long bones and the tibia is the most frequent site.

In skeletal syphilis the lesions are of two main varieties: periostitis and osteochondritis. As a rule both forms are present.

The roentgenograms show characteristic changes—periostitis for example with one or more shadows parallel to the cortex. There is excessive and rapid subperiosteal bone overgrowth. The original cortex is ordinarily thin and irregular. In the congenital variety there is a variable osteochondritis, periostitis and arthropathy. Serologic tests are obviously necessary.

LYMPHOMA AND LYMPHOBLASTOMA This condition may produce cystic destructive lesions of bone (and infrequently bone condensation) usually in the spine. In sequence of incidence the bones ordinarily affected are spine, sternum, pelvis, femur, ribs, skull, humerus, scapula, clavicle and tibia (Figs. 378 to 380). The involvement has a dis-

tribution which parallels that of metastatic cancer

The alkaline serum phosphatase may be elevated

LEUKEMIA. There are signs of moderate bone destruction infiltration and expansion of the marrow cavity atrophy of the cortex, demineralization and new bone formation parallel with the shaft in several long bones (Figs 376 to 377) The presence of a high percentage of myeloblasts or lymphoblasts in the blood and the bone marrow is characteristic. Sternal puncture is especially of value in aleukemic persons

The following four varieties of bone lesions are seen in leukemia (a) transverse bands of decreased density at the ends of the shaft of the long bones (b) destructive (c) clerotic (rare) and (d) subperiosteal formation of new osseous tissue

In chronic myelogenous and lymphatic leukemia there is a progression ordinarily of the hypochromic variety

CHLOROMA. This is a variant of myelogenous leukemia with formation of pale green tumors (when fresh) Tumors may form in the skin or in the bones of the skull The masses are found contiguous to the periosteum of the bones of the face the ribs the sternum or the vertebrae and less commonly in the viscera On microscopic examination the tumors are found to be composed of myeloblastic cells. Sternal puncture helps in the differentiation from polyostotic fibrous dysplasia.

ECHINOCOCCUS CYST OF BONE. This is an extremely rare disease found in the United States and elsewhere in North America The vertebrae appear to be the site of predilection The lesions are multilocular polycystic and without productive reaction or calcification The surrounding bone is thin and expanded The intradermal Casoni or Culbertson and Rose tests are positive

LEONTIASIS OSSEA. This condition rarely needs differentiation because it is hardly a disease per se but rather a roentgenographic pattern of the skull which may be found in a variety of diseases such as Paget's disease even including polyostotic fibrous dysplasia.

In leontiasis ossea there are symmetric hyperostoses of the facial bones and the skull which encroach upon the cranial cavity (Fig 290)

ACHONDROPLASIA. Achondroplasia is a rare congenital condition in infancy leading to dwarfism and generalized deformity There is a generalized symmetric abbreviation of the diaphyses with great thickening of the epiphyses causing enlargement of the articulations which are attributable to hyperplasia of the cartilaginous ends of the bones. The trunk is of normal dimensions. The cranium is large and the face contrastingly small There are diminished density hypoplasia thinning and wedging of the vertebrae The union of the epiphyses of the long bones may be premature normal or late (Figs 73 to 76)

Achondroplasia seldom causes doubt if the characteristic shortening of both arms and legs the facies and the trident hand are kept in mind. The roentgenographic features are also diagnostic.

OSTEOGENESIS IMPERFECTA. This condition often presents blue sclerae and sometimes certain other hereditary evidences which appear to be significant in differential diagnosis however blue sclerae occasionally have been reported in association with polyostotic fibrous dysplasia.¹⁷

On roentgenographic examination many healed fractures and angulations are seen. The compacta is osteoporotic and thinned trabeculations appear to be missing (Figs 19 to 22) The osteocartilaginous margins reveal a provisional zone of calcification

MONOSTOTIC FIBROUS DYSPLASIA. The sites of predilection for monostotic forms of fibrous dysplasia are the proximal metaphysis of the femur the ribs, the jaw bones and the tibiae. As a rule the first indication of the disease is a local swelling particularly if the affected bone is superficial There is local tenderness sometimes associated with the tumor and sometimes the pain is of an arthritic nature

In contrast with the reported cases of Albright's disease one of the patients shows abnormal pigmentation or evidence of pre-

cocious puberty. The lesion grows insidiously or remains stationary. No congenital abnormalities are found.

Complications. Fractures are common but unite readily. Nonunion may be noted with severe coxa vara.

Acromegalic features and severe failure of vision have been reported. There have been a number of reports of bone sarcoma supervening on lesions in Albright's disease. They are usually non bone forming pleomorphic nodule and giant-cell sarcomas.

Bamatter¹ from the Fanconi Clinic reported the case of an 11 year-old girl suffering from polyostotic fibrous dysplasia complicated by purpura. In discussing this report Fanconi stated his belief that there was a close correlation between bone marrow and fibrinogen formation.

Congenital arteriovenous aneurysm was cited by Stauffer¹² as a complication of polyostotic fibrous dysplasia.

Treatment. The only known effective treatment of fibrous dysplasia is surgery (Figs 34 to 36). It may be indicated where one or more of three conditions is present: (a) continued pain in the area of a localized bone lesion, (b) fracture through a lesion or (c) severe bowing as a result of spontaneous fracture.

Surgery also is difficult here and subject to complications. For instance osteotomy of the shepherd's-crook deformity may be done and healing in corrected position occur. Then a subsequent deformity will develop. Cysts may be filled in with bone chips and then these bone chips found to be reabsorbed subsequently. A safer technic is resection of the involved area, intramedullary fixation and use of much bone to replace the resected portion.

Hemiresection with intramedullary nailing of the involved long bone to maintain length and alignment and prevent fracture has been done by DePalma.¹⁰

Bone chips are used to replace the resected half of the involved area. Later when consolidation of the new bone has occurred resection of the remaining portion of the lesion is carried out with chip replacement.

Prognosis. In young persons polyostotic fibrous dysplasia may be progressive. Later in life it tends to remain stationary. Deformities of the chest with compression of the lungs or the heart may place the patient's life in jeopardy.

SOLITARY (UNICAMERAL) BONE CYST

Historical Notes. The first example of unicameral bone cyst was reported by Virchow¹ in 1876 as an accidental postmortem finding. For many years solitary bone cysts were included in the group of fibrocystic diseases of bone. Reviews of this subject by Bloodgood² in 1910 and by Emslie³ in 1914 were authoritative at the time they were written. Heineke⁴ initially described the roentgen features of this entity.

Today the various fibrocystic lesions of bone have been delineated carefully. The well known entities of hyperparathyroidism (osteitis fibrosa cystica generalisata), fibrous dysplasia and giant-cell tumor are among the principal entities that have been differentiated. Therefore as a result of both the separation of these other entities and specific investigations on solitary bone cyst itself a definite entity has emerged.

Clinical Features. A solitary osteolytic lesion is found near the epiphyseal plate in the metaphysis of a long bone in a child of 3 to 15 years of age. Pain resulting from a pathologic fracture in the area of the bone lesion is the usual presenting symptom (Figs 41 and 43). This in turn furnishes the impetus for radiographic examination. Occasionally the bone cyst may be found incidentally in the humerus on a chest radiogram.

Pathogenesis. No definite conclusions as yet have been reached as to the etiology of this lesion. It is not frequent in incidence but occurs often enough to have caused most workers to give some thought to its origin. Most authorities accept the close proximity of the solitary bone cyst to the epiphyseal plate of the young child. Later growth results in the migration of the cystic lesion



FIG 40 Typical unicameral cyst in metaphyseal or active position in humerus

from the metaphysis to the mid-shaft. Yet one of the authors⁶ has been able to report the existence of a solitary bone cyst in the mid-shaft of a humerus in a child aged 5 years.

Some of the various theories of origin of this lesion are as follows

Pommer⁴ advanced the view that solitary bone cyst resulted from intramedullary hemorrhage. It was his thought that the traumatic hematoma caused localized bone reabsorption. It is possible that some of his cases were those of hyperparathyroidism. Modern-day workers have found very few osteoclasts in a bone cyst. Moreover these are usually the result of hemorrhage secondary to pathologic fracture. It is also noteworthy that true bone cysts are not seen in hemophilia.

Plemister and Gordon⁷ sought to establish an infectious etiology of this lesion. They cited two cases in which anaerobic *Streptococcus viridans* was isolated. Subsequent workers have not been able to confirm their findings.

Bone infarction has been suggested as the etiologic basis for unicameral cyst. However



FIG 41 Unicameral cyst in latent position in the humeral shaft. White male 9 years old. Left humerus. There is a fracture with deformity through the cyst with some healing reaction

microscopic examination of the lesions of callosan disease or Gaucher's disease complicated by bone infarction, reveal these lesions to be entirely different histologically from unicameral bone cyst.

Geschickter and Copeland⁸ favor the theory of progressive osteoclastic proliferation at the metaphyseal-epiphyseal junction as the etiologic basis for solitary bone cyst and giant-cell tumor. They note that about 75 per cent of their cases of bone cyst show a predilection for the upper end of the humerus, the femur or the tibia. They also note that with advancing age the cyst will migrate from its metaphyseal position into the so-called latent area of the mid-shaft.



FIG. 42 Unicameral bone cyst in the upper metaphyseal region of the femur. Balance studies revealed no loss of calcium or phosphorus. A calcifying regimen had no effect on the lesion. The only therapeutic approach is surgical.



FIG. 43 Unicameral bone cyst. White male whose difficulty began at age 7 in 1944. Right femur. Anteroposterior and lateral views made in December 1944, 1 month after pathologic fracture through the proximal portion of a bone cyst at the distal metaphysis of the right femur. The multiloculations represent cortical ridging, not true septa. There is evidence of healing in response to the fracture. Biopsy immediately after these films was compatible with the diagnosis of solitary bone cyst. Treatment of the fracture by another surgeon was by plaster and later by Thomas caliper brace immobilization.

Jaffe and Lichtenstein⁶ have revived Mikulicz theory of the bone cyst being a localized osseous dystrophy. They do not agree that the causative cell is the osteoclast as advocated by Geschickter and Copeland but feel that it is a cell called into action only as a result of the original osteolytic manifestation of the lesion. Moreover, further osteoclasts are found as a result of the hemorrhage accompanying the pathologic fracture so frequently seen in this entity.

RADIOGRAPHIC FINDINGS. A typical lesion is found in the metaphysis, particularly of the upper humerus (Fig. 40), the upper fe-

mur (Figs. 42 and 43) or the upper tibia. There is an area of localized bone destruction in the metaphysis. There is frequently a fusiform expansion of the cortex at the site of the defect. The cortical bone is somewhat thinned.

The cyst may appear to be truly unicameral (Fig. 40) or there may be trabeculae visualized in the x-ray picture (Figs. 42 and 43). As noted above, these do not represent septa through the lesion but merely ridging of the cortex as a result of the expansion of the cystic defect.



FIG 44 Unicameral bone cyst. (Same patient as Fig. 43.) Right lower femur. X-ray pictures in May 1943, reveal some filling in of the cyst by healing reaction but the distal end of the lesion looks suspiciously active. No curettage had been carried out.

There is an open epiphyseal plate found close to the lesion in those cases found in childhood and adolescence (Figs. 40-42, 43). If the lesion is found as an incidental radiographic discovery there may be no evidence of pathologic fracture. In the more typical case however actual fracture or more rarely minute infraction of the cortex on one side of the cystic area is present.

With advancing age the cyst will migrate away from its so-called active position in the metaphyseal region to a latent position in the middiaphysis* (Figs. 41 and 47).

Pathology. The bone overlying the cystic area may be enlarged in circumference as a result of the expansion of the cyst. However the cortex itself may be thinner than normal. It may be lightly ridged by the smooth connective tissue membrane of the cyst.



FIG 45 Unicameral bone cyst. (Same patient as Fig. 43.) By August, 1946, X-ray pictures of the involved right femur show definite reactivation of growth in the cyst. Skeletal roentgenographic survey was negative. Blood chemical studies including calcium, phosphorus, and alkaline phosphatase, were normal.

This lining may or may not be complete throughout the entire circumference of the lesion. The cyst will contain a clear yellow fluid but it may be blood-stained in the presence of recent fracture.

In the surrounding bone there may be evidence of a healing reaction (Figs. 41 and 43). There may be periosteal lifting with new bone formation particularly if there has been a fracture.

The surprising finding is the minimal amount of connective-tissue elements obtained by curettage.



FIG. 46 Unicameral bone cyst. (Same patient as Fig. 43.) In December 1946 operative curettage and filling in of the cavity with pelvic bone chips was carried out. The cyst was still in the active position and care had to be taken to spare the epiphyseal plate. X-ray pictures of the lower right femur in March 1947 demonstrate the healing reaction following definitive surgery.



FIG. 47 Unicameral bone cyst. (Same patient as Fig. 43.) Lower right femur X-ray pictures in October 1952 reveal satisfactory evidence of complete healing. The sclerotic area has migrated away from the metaphyseal area to a latent position in the diaphysis.

There are no septa. Any loculation visualized on the x-ray picture is actually the presence of cortical ridging rather than any compartmentation of the lesion itself (Figs. 42 and 43).

MICROSCOPIC FEATURES Microscopic features include the thin connective tissue membrane. In its wall are found the osteoblasts giving rise to some new bone formation.

The controversial cell in this lesion is the giant cell found in some number in histologic sections of various unicameral bone cysts. Geschickter and Copeland⁸ feel that the giant cell represents a definite causative lesion-cell entity. They believe it is related to osteoclastoma or giant-cell tumor which is seen in a later age after closure of the epiphyseal line. They believe that the giant cells found are primary in the tissue of the bone cyst.

On the contrary Jaffe and Lichtenstein⁹ feel that the osteoclasts or giant cells are present merely as a response to bone destruction in association with the lesion. In addition a further osteoclastic response is called out as a result of bone pathologic fracture. Furthermore phagocytic cells are found because of blood elements found in the tissues following cortical infraction. They feel that the giant cell of this lesion is entirely different from the tumor giant cell of the osteoclastoma or giant-cell tumor.

Treatment. This is a benign lesion with out any tendency to local spread or distant metastasis. The treatment of choice is operative curettage, bone graft and bone-chip implantation (Figs. 46 and 47). The use of escharotic agents such as concentrated zinc chloride solution following curettage, is favored by some surgeons.

Some workers^{10, 11} have noted a tendency



FIG 51 Enchondroma of the first metacarpal in an adolescent patient. Differential diagnosis for this type of lesion includes bone cyst, giant-cell tumor, tuberculosis, syphilis, and osteoid osteoma.

chondromas is the interior of the phalanges and the metacarpals of the hand (Fig 51). They also occur as single tumors inside the metaphysis or even the diaphysis of long bones (Figs 49 and 50). Here they may grow enormously.

Occasionally they may involve the endochondral bones of the pelvis and the scapula. Whenever the pelvis and the scapula are involved malignant variation must be suspected.

It has been thought that the ribs and the vertebrae also may be involved by this tumor¹ (Fig 48). However, some feel that this never occurs.² The involvement of a rib



FIG 52 Osteoid osteoma simulating metacarpal enchondroma. (From Dr M. M. Pomeranz.)

has been demonstrated in some cases to be the superimposition of an osteochondroma (Fig 62). The vertebral type is probably a Schmorl nodule of herniated intervertebral disk tissue.

Clinical Features; SIGNS AND SYMPTOMS. Patients afflicted with chondroma may notice an unusual localized swelling, tenderness or pulsation. They may have localized discomfort, pain or disability. Spontaneous fracture may occur particularly in enchondroma of the hands or the feet. It is uncommon in involvement of long bones except when malignancy has occurred, but then severe pain and rapid cortical erosion and extension of the tumor occur.

The symptoms induced in the benign form are attributable to displacement of contiguous tissues and to disability from the size of the tumor.

Simple chondromas may be symptomless. Pain when present is usually inconstant and mild. Sometimes the diagnosis may be made simply by random roentgenographic study.

CHEMICAL DATA. Chondromas do not show

characteristic chemical changes in the blood serum or the urine. Malignant degeneration is not reflected consistently in elevation of alkaline phosphatase.

ROENTGENOGRAPHIC DIAGNOSIS. In the small bones of the hands and the feet the tumor will appear as an ovoid expansile osteolytic lesion (Figs 51 and 52). The appearance in the limb bones is similar except that the lesion is larger. The cortex may become thinned bulging or fractured. The rarefaction is due not to an empty space in bone substance but to radiolucent cartilage islands which displace normal bone structure. Septae therefore are not apparent on the roentgenogram. However stippled or blotchy calcification may be present and is diagnostic when present (Fig 50).

Pathology: GROSS APPEARANCE. Gross examination shows a cartilage mass with some times myxoid portions. In general, enchondroma appears largely as a bluish white lobulated cartilaginous mass. Scattered through it may be found yellow gritty tissue which is calcified and ossified cartilage.

MICROSCOPIC APPEARANCE. This shows sheets of hyaline cartilage. There is considerable cellularity with mitosis in some areas. It has been aptly said⁴ that tumors in long bones look benign and are apt to become malignant whereas tumors in small bones appear malignant microscopically and usually are benign. Nevertheless malignant degeneration is clearly demonstrated by cellular pleomorphism in contrast with the uniformly small chondrocytes of the benign variety.

The tumor is composed of hyaline cartilage calcified in a few scattered areas. In intersecting strands of fibrous tissue fetal cartilage cells are present in a myxomatous background.

Differential Diagnosis. Most important things to differentiate in small bones are in inflammatory process, osteoid osteomas, solitary cysts or giant-cell tumors (Fig 52). A solitary enchondroma is the most common single tumor of the small bones of the hands and the feet (Fig 51).

In the long bones, an uncalcified enchondroma may be confused with giant-cell tumor, monostotic fibrous dysplasia and unicameral bone cyst (Figs 42 and 49).

Biopsy of course is the ideal diagnostic method. If the tumor has expanded to involve much of the bone shaft and to produce fracture or indicate impending fracture surgery and therefore biopsy is imperative.

Complications. Malignant cartilaginous tumors may arise from an enchondroma.

Malignant changes occurring in a chondroma frequently are preceded by a period of quiescence that may extend for 20 to 30 years or even longer.

Chondrosarcoma may be grouped as follows: (a) the primary chondroblastic sarcoma that is noted in children and young adults and that resembles osteogenic sarcoma clinically and roentgenographically and (b) the secondary chondrosarcoma (chondromyxosarcoma). The latter tumors arise in an area that is the site of either a pre-existent enchondroma or an osteochondroma. Usually they develop in middle or late adult life.

The progress of either form of chondrosarcoma is characteristically slower than that of osteogenic sarcoma, and metastases occur late in the disease. Secondary nodules usually appear first in the lung and rarely in other organs. In some examples autopsy discloses a continuous intravascular growth from the tumor.

Treatment. These lesions are not radio-sensitive. The best treatment is through curettage and replacement with packed bone chips or with a fashioned solid bone graft. In certain instances where it has extended or where malignant degeneration is evident resection or ablation may be required.

MULTIPLE ENDOCHONDROMATOSIS

Definition. This is a developmental error which is characterized by multiple cartilaginous tumors in the long bones which may vary from a few bones to all of the long bones which may be widespread and bi-

lateral or which may be predominantly unilateral (Figs 53 to 59)

Historical Notes. The predominantly unilateral form has been described by Ollier and is termed Ollier's disease. It is distinctly questionable, however, that cases are distinctly unilateral even one of Ollier's original cases had bilateral manifestations.*

Ollier also described earlier several cases

of hereditary multiple exostoses and his name has been given to this entity also.* The authors prefer the descriptive terms for both entities and avoid the confusion eponymic designation. Moreover the term dyschondroplasia is also nonspecific and seems less useful than the designation multiple enchondromatosis which clearly indicates the pathologic origin.

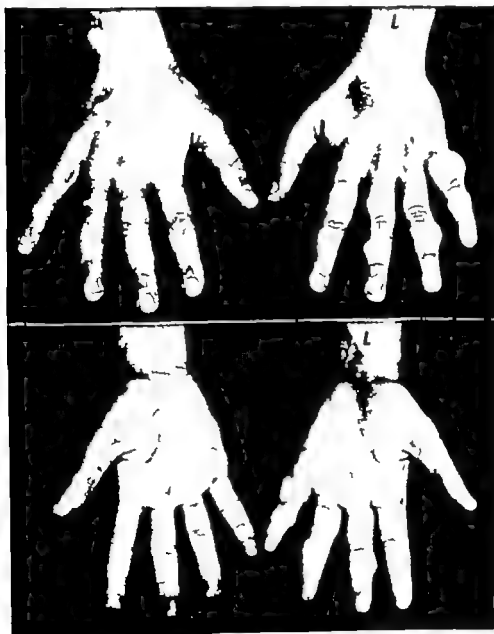


FIG 53 Multiple enchondromatosis. (Figs 53, 54 from Dr M M Pomeranz) Both hands, showing the multiple knobby changes predominating on the left side.

Incidence This disease apparently is not hereditary but is a developmental defect. Either sex may be affected; the male slightly more than the female. The disease begins in infancy but may not be detected until much later unless severe multiple deformities are manifested. It is rarer than the solitary form.

Clinical Features. The degree of involvement varies from a case with only a few bodies involved to one in which many, even all of the limb bones are involved (Fig. 53). The epiphyses are more apt to be af-

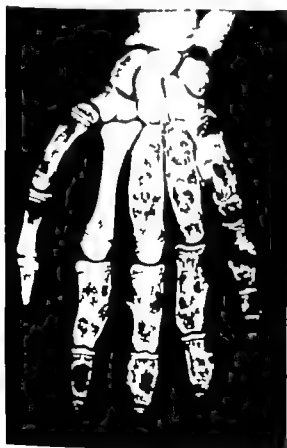
fected in this condition so that it may be characterized by growth disturbances.

Pathology: Gross Appearance. This shows lobulated cartilaginous masses within the metaphysis and the diaphyses. They appear to arise at the metaphyseal side of the epiphyseal plate. No bone trabeculations are evident but ossified and calcified cartilage is present.

Microscopic Appearance. Microscopic findings are hyaline cartilage masses with some variation in the uniformity of cell size. Mitosis may be present. There is greater

FIG. 54 (Left) Multiple enchondromatosis (Same patient as Fig. 53) Left hand. X-ray picture confirms photographic evidence of knobbing shown in Figure 53. Widespread metacarpal and phalangeal cartilaginous lesions without calcification. Histologic pleomorphism in these lesions is at variance with the usual benignity and makes the detection of occasional malignant superimposition difficult.

FIG. 55 (Right) Multiple enchondromatosis (Ollier's disease) (Figs. 55-56 from Dr. M. V. Pomeranz) Right upper extremity lesions are present in the lower humerus and the radius.



profuseness of cells than in the solitary form. Malignant degeneration is more apt to occur in this type.

Treatment. Treatment involves attention to all of the involved areas with steps taken for each as changes in the single form indicate. The multiplicity of the condition means inability definitively to handle this condition as the solitary form can be handled.

Prognosis. Chondrosarcomatous degeneration of these tumors is much more likely than in the solitary type. This may occur even at multiple sites.

MAFFUCCI'S SYNDROME

Definition. This is multiple enchondromatosis or dyschondroplasia with multiple soft tissue hemangiomas.

Historical Notes. This condition was first reported by Maffucci.⁷ Of the two compo-

nents of the syndrome, the dyschondroplasia is similar to Ollier's disease⁸ and the vascular abnormalities in the forms of cavernous hemangiomas and phlebectasia appear to be coincidental.

Incidence. The condition is nearly three times as frequent in males as in females and usually is not recognized until late childhood.

Clinical Features. During the years before puberty a hard nodule appears unilaterally or asymmetrically most commonly on a finger or toe. This is soon followed by others involving the extremities and the limbs.

Dilated veins and soft bluish tumors appear on the involved limbs and the trunk. Fractures of one or more bones may follow slight injury. Union is slow. It may be noted that development is uneven on the two sides of the body. One whole side of the child may remain dwarfed and de-

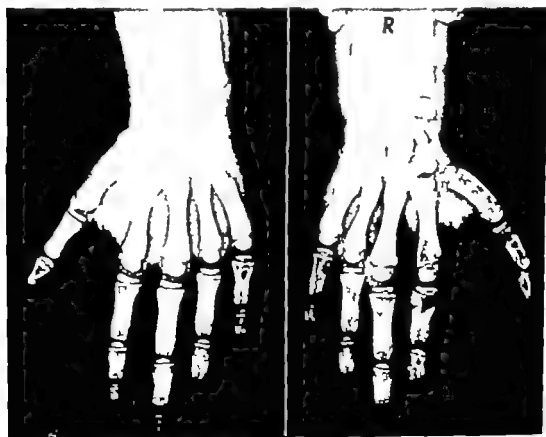


FIG. 56. Multiple enchondromatosis (Ollier's disease). (Same patient as Fig. 55.) Widespread involvement of both hands with more advanced changes on the right side.

formed. The curved uneven bones induce secondary deformities such as genu valgum pes planus etc. Throughout the period of development the deformities increase in degree.

In severe examples of the syndrome the hands and the feet become almost unrecognizable and are changed into large masses of tumor growth in which only the protrusion of a nail shows the presence of a digit.

Pathology. The bone lesions are enchondromatous rather than osteochondromatous and are characterized by irregular expansion of the cortex and widening of the shaft.

The hemangiomas may occur in the subcutaneous tissue but have also been noted in the lips the palate and the mesocolon. They form blue or reddish blue tumors which are soft and compressible and sometimes tender on pressure.

Thrombi may form and occasionally be-

come calcified as phleboliths they produce a pronounced radiographic pattern in the soft tissues.

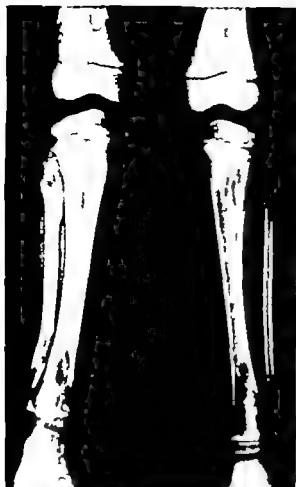
Phlebectasia is common and may affect large groups of veins or be confined to a few areas in a vein causing beadlike swellings.

GROSS APPEARANCE. The small bones of the hands and the feet (but not the carpals and the tarsals) are the site of multiple small cystic areas (enchondromas) with irregular expansion of the cortex and widening of the shaft. The bones are thus quite irregular in outline. Similar areas may be seen in the long bones and occasionally in the ribs the scapulae and the vertebrae.

MICROSCOPIC APPEARANCE. Microscopic examination indicates that the dyschondroplasia results from failure of absorption of the cartilaginous growth plate of the epiphysis.



FIG. 57 Multiple enchondromatosis (Ollier's disease) (Figs. 57 to 59 from Dr. M. M. Pomeranz). Pelvis. Anteroposterior view. Bilateral upper femoral lesions with additional lesion in the left ilium. Note the spina bifida of the first sacral segment.



OSTEOCARTILAGINOUS EXOSTOSES

Definition. Osteocartilaginous exostoses are cartilage-covered cancellous extrusions of bone found most often at the metaphysis of long bones but also found on flat bones.

The disease may occur in solitary or multiple forms. The solitary form is usually termed an *osteochondroma*; it represents the most common benign tumor of bone (Figs 60 to 64). The multiple form is usually hereditary and is more apt to develop malignant degeneration or deformity. The latter has many synonyms: Ehrenfried's

FIG 58 (*Left*) Multiple enchondromatosis (Ollier's disease) (Same patient as Fig 57) Both lower extremities. Anteroposterior view. Bilateral involvement with predominant changes on the right. The lesions appear to be concentrated at the metaphyses.

FIG 59 (*Bottom*) Multiple enchondromatosis (Ollier's disease) (Same patient as Fig 57) Bilateral foot involvement with slight predominance of right-sided lesions. The x-ray pictures are transposed.





FIG. 60 Osteocartilaginous exostosis. White male 13 years old. Right knee. Anteroposterior and lateral views. The sessile type of osteochondroma of the lateral aspect of the upper tibia is visible in the anteroposterior view. In the lateral view the lesion simulates an enchondroma.

disease¹ hereditary multiple exostosis
multiple hereditary osteochondromatosis
metaphyseal aclasis diaphyseal aclasis
(Keith, 1920)² dyschondroplasia³ heredi-
tary deforming chondrodysplasia exostotic
dysplasia exostosi osteogenetische ecchon-
drosis ossificans multiple osteomatosis
chondral osteoma exostosis disease

Although the solitary form is the most common type of bone tumor it may be considered to be a single unit of the hereditary multiple form. Therefore the discussion for the multiple form will suffice to describe a solitary lesion except as otherwise noted.

Historical Notes Klenbock⁴ made the first thorough differentiation of multiple cartilaginous exostoses.

Sir Arthur Keith⁵ wrote

The name I propose one suggested to me by Mr Morley Roberts is diaphyseal aclasis because the main incidence of the disturbance falls upon the modeling or pruning of the diaphyses or shafts of the bone. It will be seen that the supposition that there is an arrest of development in the periosteal ring of the diaphyseal growth disk explains the appear-



FIG. 61 Osteocartilaginous exostosis. White male 12 years old. Left knee. Anteroposterior view. Pedunculated type of osteochondroma arising from the medial aspect of the proximal tibial metaphysis. Contrast with Figure 60.



FIG 62 Osteocartilaginous exostosis or osteochondroma. White male, 87 years old. The lesion arises from the proximal portion of the right twelfth rib. Note erosion of the eleventh rib. There is calcification of the cartilaginous portion of this long standing tumor which has remained unchanged in size and appearance for many years.



FIG 64 Osteochondroma. Advanced calcification is present in an enormous lesion originating from the scapula.



FIG 63 Osteochondroma. Moderate calcific stippling is present in the lesion arising from the iliac wing.

ance presented by the shafts of long bones in diaphyseal aclasis.

The arrest in the extension of the periosteal ring permits the cartilage of the diaphyseal disk to become exposed on the surface of the shaft and thus leaves it uncovered and free to give rise to irregular outgrowths or exostoses. A covering of periosteal bone maintains a restrictive influence on endochondral bone.

In 1930 Müller denied the importance of the epiphyseal plate in this disease which he considered took origin in a constitutional anomaly of the perichondrium or the periosteum.

Incidence. Males are affected about three times as often as females. The upper metaphysis of the tibia and the lower metaphysis of the femur are affected most commonly, the lower end of the tibia and the fibula next. This is true for both the solitary and the multiple types (Figs 60, 61 and 71). The exostoses are bony hard and fracture of an exostosis occasionally occurs.

Etiology The etiologic factors are still a matter of divergent opinion. A reasonable hypothesis was advanced by Keith² in indicating failure in the modeling process of bone. The authors consider this to be part of the explanation.

Exostoses are peculiarly related to areas in which endochondral bone formation occurs. Replacement of the cartilage mold by bone is the function of the perichondral splint (Fig. 7). A defect at a superior or an inferior metaphyseal edge of this splint would mean incomplete replacement of cartilage by bone at that point. Modeling of bone will occur throughout the rest of that bone but will be interfered with at the site of the cartilage overgrowth. The cartilagi-



FIG. 65 Chondrosarcoma arising from pre-existing osteocartilaginous exostosis of the tibia. (From Dr M. M. Pomeranz.) The malignant supervention occurs in the cartilage cap of the osteochondroma.



FIG. 66 Hereditary multiple exostoses or diaphyseal aclasis. (Figs. 66 to 72 from Dr Harold J. Isard and Dr S. S. Mintz.) White male, 20 years old. Both shoulders. Anteroposterior views. Multiple osteocartilaginous exostoses of the proximal humeri and the scapulae. The scapular lesions are heavily calcified at the cartilage cap. The right humerus is involved more severely than the left.



FIG 67 Hereditary multiple exostoses or diaphyseal aclasia. (Same patient as Fig. 66) Left scapula in profile to demonstrate osteochondroma arising from just above the inferior angle. Such a lesion can be misconstrued as an enchondroma if not seen in oblique view.



FIG 68 Hereditary multiple exostoses or diaphyseal aclasia. (Same patient as Fig. 66) Both forearms. Anteroposterior view. The left radius and the ulna are bowed. There are sessile exostoses in the diaphysis of the left ulna, with shortening.

nous excrescence maintains some of the growth potentiality of the epiphyseal plate; therefore bone will lay down in a part of this excrescence (Figs. 62 to 64).

Clinical Features. SIGNS AND SYMPTOMS OF THE MULTIPLE FORM. The multiple form of the disease is hereditary. It develops insidiously during childhood, afflicting males more often than females.

Hereditary multiple exostoses are characterized clinically by the slow evolution and growth of many protuberances on different bones; the number in some reported examples has reached a few hundred. The most frequent site is the metaphyseal area at the knees, the ankles, the shoulders, the scapulae, the pelvic bones, the ribs, the vertebrae, the metacarpals and the metatarsals (Figs. 66 to 68). The bones of the skull are involved rarely.

The exostoses are symmetric, as a rule. Unilateral development is uncommon. Growth of the exostoses parallels skeletal growth. In severe examples of the multiple form the growth of the skeleton, especially the long bones, is affected so that deformities develop. Common growth disturbances are relative shortness of the ulna and the fibula (Figs. 68, 69 and 72).

These tumors seldom give rise to symptoms owing to their slow growth. Sometimes they interfere with free tendon action, resulting in snapping tendons. At times a bursa develops over their apex and becomes inflamed (Fig. 71).

Malignant degeneration* may occur in the multiple form less commonly in the solitary form. Pain and rapid growth suggest malignancy (Fig. 65).

CHEMISTRY. The chemical constituents of

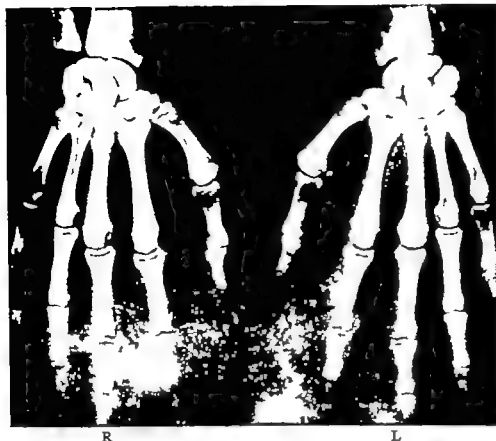


FIG. 69 Hereditary multiple exostoses or diaphyseal aclasis (Same patient as Fig. 66) Both wrists. Anteroposterior view. The shortened and deformed distal left ulna is shown. There are a pedunculated exostosis of the distal right ulna and a sessile lesion of the distal right radius with little deformity. In this instance the hands are spared but severe examples may have outgrowths on both metacarpals and phalanges.

the blood serum and of the urine remain unchanged as a rule.

ROENTGENOGRAPHIC APPEARANCE. Cartilaginous exostoses consist externally of compact, and internally of a spongy structure. The latter in the shaft of involved bone is continuous with that of the exostosis. The appearance of the cartilage cap varies in size and degree of calcification (Figs. 63, 64, 66, and 67).

The base of the offshoot may be narrow or broad. The offshoot is seen either at a right angle to the shaft or inclining toward the diaphysis (Figs. 60, 61, and 71). Large exostoses sometimes displace adjacent bones or produce erosion by pressure (Fig. 62).

The salient feature of the roentgenogram is the bony projection from the metaphysis. The apex of the projection, as previously stated, always points away from the nearest

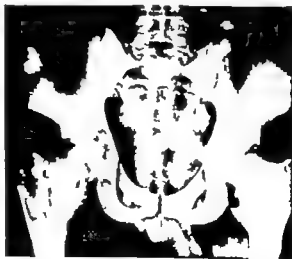


FIG. 70 Hereditary multiple exostoses or diaphyseal aclasis (Same patient as Fig. 66) Pelvis and upper femora. Anteroposterior view. Pedunculated bony outgrowths are found arising from the right iliac wing and both proximal femora.



FIG 71 Hereditary multiple exostoses or diaphyseal aclasis. (Same patient as Fig 66.) Both knees. Anteroposterior view. Here involvement is severest. There is lack of proper modeling bilaterally more on the left. Note the clubbed shape of the femora and the abnormal fibulae. Multiple exostoses sessile and pedunculated originate from the femoral, the tibial and the fibular metaphyses. Bursae may develop over these larger lesions.



FIG 72 Hereditary multiple exostoses or diaphyseal aclasis. (Same patient as Fig 66.) Both legs. Anteroposterior view. Severe bilateral developmental abnormalities can be seen involving both the tibiae and the fibulae. Most of these exostoses are sessile in configuration.

epiphysis. The terminal segments of the affected shafts particularly in the hereditary form are larger than normal thereby making an apparently long metaphysis. Deformities may be seen in the forearm or leg in the multiple hereditary type (Figs 68 and 72). In some examples there may be longitudinal striations in the metaphysis similar to those in osteopathia striata. In others again there may be punctuated shadows of increased density presumably of the same character as those seen in osteopolkilosis.

Pathology. **MACROSCOPIC APPEARANCE.** The growths are pearl blue or yellow and

show a rubberlike consistency. The shape of the exostosis may be sessile (against the bone) or stalked. The exostosis may vary in size.

MICROSCOPIC APPEARANCE. The histologic characteristics are those of an ossifying enchondroma or exostosis which breaks the normal osseous contour. The superimposed pointed cap is composed of undifferentiated cartilage. The base of the exostosis is covered by periosteum. As time progresses the cartilage cap thins; reactivation of the cap is suggestive of malignant degeneration (chondrosarcoma). The cap projects in a slanting direction away from the adjacent joint.

Diagnosis. There is little difficulty when the offshoots are large enough to be palpable. Sometimes they are discernible only by radiographic examination if solitary or small.

Complications. Some of the complications which may be discovered are (a) interference with joint function (b) pressure on nerves and blood vessels (c) local inflammation (d) fracture of pedicle of the exostosis and (e) chondrosarcomatous change.

Treatment. Surgical excision is indicated when an exostosis interferes with movements of a joint or the action of tendons or when it impinges upon a nerve. When ma-

lignant degeneration occurs wide resection or ablation is indicated.

Prognosis. Exostoses commonly cease to grow with skeletal maturation. On rare occasions there are malignant changes within the cap of the exostosis. This is more common in the hereditary multiple variety than in the solitary example.

ACHONDROPLASIA

(Syn Chondrodystrophia foetalis mi cromelia)

Definition. Achondroplasia is a developmental error resulting in disturbed endo-

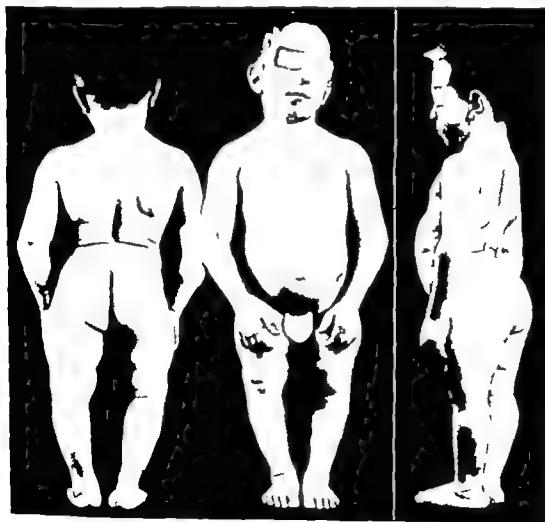


FIG. 73 Achondroplasia. (Figs. 73 to 76 from Dr. M. M. Pomeranz.) Typical achondroplastic dwarf. The photographs show moderate brachycephaly, foreshortened limbs in relation to the trunk, increased lumbar lordosis and bowing of the extremities.

The hand is a trident hand because the middle finger is the same length as the index and the ring fingers

The middle phalanx of all the fingers is shorter than normal in relation to the other phalanges. The upper arm is short in proportion to the forearm. Both upper and lower extremities are considerably shorter and thicker than normal

Limitation of joint movement is a common phenomenon. The upper limbs do not fall completely to the side and with their shortening this tends to make the arms stand away from the side in this strange fixed stiffened way. Elbow extension is usually limited. The lower extremities show bowing of the legs often due to curvature of the tibiae. There is calf bow. There is sometimes hyperextension of the knee. The head of the fibula is placed abnormally high. The bowing of the lower extremities gives a suggestion that coxa vara may be present in the hips but this is not so

Pathology The principal sites of pathologic disturbance are at the epiphyseal plates of the long bones at the base of the skull and at the epiphyseal plates of the ribs

The primary problem occurs at the zone of provisional calcification of the epiphyseal plate. This may vary from simple retardation to practically complete aplasia. The cartilage columns in the zone of provisional calcification do not proliferate and line up in an orderly fashion. Calcification occurs in a spotty way in these irregular cartilaginous masses which are then not properly absorbed and replaced by bone

The principal defect is thus the lack of normal chondrocyte growth and development at the proliferative zone of the epiphyseal plate. It is this area which normally gives rise to cartilage columns which later become calcified thereby making them more easily reabsorbed and available for bone replacement

Since these chondrocytes are not developed in adequate numbers or quality the process of bone development is retarded or ceases at this point

When growth stops the epiphyseal may remain in situ or may be obliterated

Base of the Skull There occurs premature fusion of the sphenoid and the occipital bones to form a shortened skull base. As a result, the foramen magnum is reduced in diameter to as much as one half of that which it usually attains in the normal individual. It is rather an interesting problem that the skull premature fusion occurs, and in this condition it is not uncommon to find epiphyseal plates that persist indefinitely on the limb bones

This appears to be a finding which has not been fully explained. It is true of course that the humerus and the rib epiphyseal plates are close in achondroplasia in early childhood but it is not the rule. At the base of the skull, premature fusion is the rule. Achromatopsia appears to have a mild degree of hydrocephalus

Similar pathologic changes occur in the vertebral column and in the ribs but these changes are less marked than in the long bones and the base of the skull so that the dwarfing is of the long bones and the base of the skull

ROENTGENOGRAPHIC FINDINGS The epiphyseal plates at the extremities are broadened at the base but are relatively normal in diameter at the distal end. They are shortened in length. The shortening appears to be proportionately greater proximally than distally which is contrary to that found in pituitary dwarfism. For instance in achondroplasia the femur is relatively shorter than the tibia than the fibula (Figs 75 and 76)

The muscular ridges of the bones are exaggerated. The tibia is shorter than the femur and that is why the fibular head is so prominent in achondroplasia (Figs. 75 and 76). The radius may be shorter than the ulna, which would cause a peculiar deviation to the hand (Fig. 74). Usually however it is the other way around so that the ulna is shorter than the radius. This discrepancy produces a bowing effect on the upper extremities.

Epiphyseal Changes by X-rays The epiphyseal centers appear enlarged but are

usually not abnormal in size. It is the flared metaphyseal end that makes them appear larger than normal. This is particularly evident in the metaphyseal end around the lower femur and the upper tibia where they may be almost V-shaped and appear to practically enclose the epiphyseal center (Figs 74 to 76).

The epiphyses of the long bones appear at the normal time or somewhat early. They may fuse or close early, normally or late.

The sternum is short, broad and thick. The ribs are shortened to less than half their usual length. The scapulae are deformed. The glenoid does not appear to be large enough for the humeral head and this accounts for some of the fixed abduction contraction. The lower border of the scapula is squared off as if the lower portion has been at the side.

The pelvis is small over all; this probably is associated with early fusion of epiphyseal lines.

The hip sockets are placed more posteriorly than is normal so that the sacrospinous notch is closely contiguous to the acetabulum. The sacrum tends to protrude considerably posteriorly, but this is probably a part of the excess lumbar lordosis.

Base of the Skull. This shows premature fusion of the presphenoid, the postsphenoid and the basisphenoid nuclei to form the os trabeculare which is abnormally short.

The mandible is essentially normal in size but because the base of the skull is shortened it appears prognathic in type.

Spine. The vertebral bodies are not particularly abnormal in size but there is a little tendency toward a smooth dorsal kyphosis sometimes associated with wedging and an increase in lumbar lordosis.

Differential Diagnosis. The deformities can be determined prenatally by x-ray picture. The findings then will be a large head and the small thickened extremities with short bones which are widened at their ends.

The condition must be differentiated from the pituitary type of dwarfism which of course shows symmetrical changes and not the disproportion as far as the head and the

limbs in relation to the trunk are concerned. The pituitary dwarf shows deficient sexual development or hypogonadism. This is not true in the case of the achondroplastic.

It must be differentiated from the primordial dwarfs who are simply small, normally proportioned and developed people. Examples of these cases are the pygmies of Africa.

The condition must also be distinguished from chondro-osteodystrophy or Morquio-Brailsford disease and Hurler's syndrome or gargoylism (Fig. 96).

The epiphyseal centers, particularly radiographically in Morquio's disease are definitely at variance (Figs. 99 to 103). The vertebral changes show the slipper tongue changes with kyphosis (Fig. 98). There is an increase in anteroposterior diameter of the chest, in contrast with that seen in achondroplastics.

In Hurler's disease there is mental deficiency, liver enlargement and corneal opacity. Moreover the last two chondro-osteodystrophic types are born normally and develop between the first and the fourth years, whereas achondroplastics may be evident even while still fetuses and certainly are well-defined at birth.

Treatment. This is a developmental defect and no specific treatment has been developed for this. As a matter of fact, the changes are irreversible when they are observed and evident.

Prognosis. The fusion of epiphyses sometimes may be delayed even until the fifth or the sixth decade in some individuals. The adults will be markedly shorter in height than the normal human being. As stated previously a considerable number of achondroplastics are stillborn or die within the first year—as many as 80 per cent or more.

Those who survive however have a good life expectancy. They can propagate but in the women the pelvic outlets are severely impaired and probably will require cesarean section. It must be borne in mind also that where at least one of the parents is achondroplastic, up to 50 per cent of the offspring may develop a similar deformity.

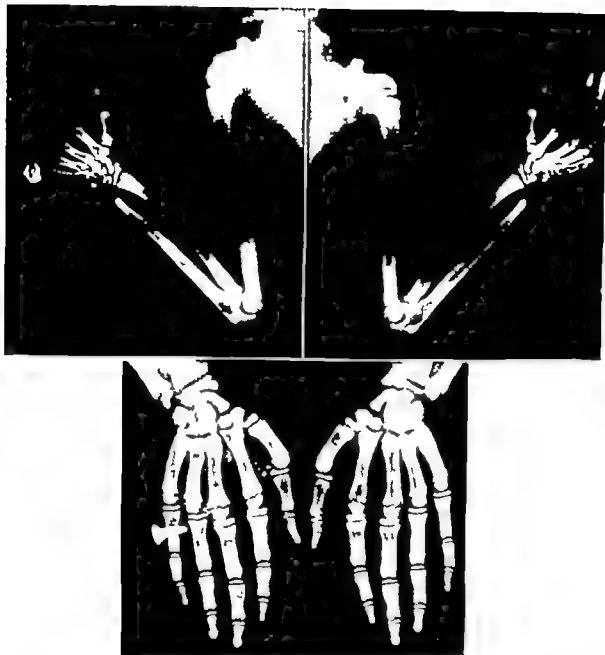


FIG 77 Osteopetrosis. (Figs. 77 to 79 from Dr. M. M. Pomeranz) (Top right) Right upper extremity. The bones are denser than normal. Zones of increased density alternate with lighter areas. (Top left) Left upper extremity. Findings are similar to those on the right side. (Bottom) Both hands. Anteroposterior view. An irregular reticulum of dense trabeculations is seen in the carpus, the metacarpals and the phalanges bilaterally. The metaphyses of the metacarpals and the phalanges are affected more than the diaphyses which appear as relatively radiolucent patches.

OSTEOPETROSIS

(Syn. Albers-Schönberg disease (1904)
osteosclerosis with anemia, marble bones,
congenital osteosclerosis, osteosclerosis
fragilis generalisata, osteosclerosis congen-

ita, diffuse morbo marmoreo, marm.
Knockenkrankheit, maladie des os mar-
rés, chalky bones (Pine), hyperostei
osteopathy, osteosclerosis disseminata,
miliaris, marboskelett, osteopetrosis fi-
gills, streifenförmige osteopolkille)



FIG 78 Osteopetrosis (Same patient as Fig 77) (Left) Rib cage and thoracic spine. Anteroposterior view. The vertebral bodies have an inferior and a superior band of increased density surrounding a central clear zone. The ribs are thickened and present streaks of increased density. (Right) Lumbar spine pelvis and hips. Anteroposterior view. Vertebral-body involvement is again well shown: there is a light central zone surrounded by two bands of increased density formed by abnormal bone. The pelvis is also typical. The iliac wings have clear zones alternating with parallel curved bands of dense bone. The acetabular areas and the upper femora are affected also.

Definition. Osteopetrosis is a rare disease beginning in infancy and even *in utero* of genetic and familial occurrence characterized essentially by an increase in the radiographic density of the bones and with varying change in structural contour. Usually the long bones tend to be shortened and clubbed at the ends with complete obliteration of the marrow cavities. The term marble bones is a misnomer. The bones are in fact, chalklike—osteocretosis or osteopetrosis is perhaps a better term.

Historical Notes. The first case of brittle bones recorded in medical literature appears to be that of Bordenave in 1763. In 1788 Eckmann (Upsala) described the familial incidence and Strack (1807) described the condition.

Albers-Schönberg¹ demonstrated generalized osteosclerosis in a living person by

means of roentgen rays. He called the disease marmorknockenkrankheit.

Reich² further analyzed the clinical picture.

Laurell and Wallgren³ introduced the name osteosclerosis fragilis generalisata.

Davis⁴ described 7 cases from the foreign literature and added 1.

Karshner⁵ introduced the term osteopetrosis in 1926.

Incidence. By 1947⁶ 148 cases had been reported. Osteopetrosis has been found in the fetus⁷ and may be present at birth or become manifest during childhood or even be observed in later life. The usual age at which it is identified is between 12 and 20 years.

Both sexes may be affected but the disease is more common in males.

Etiology. The etiology is unknown, how



FIG 79 Osteopetrosis. (Same patient as Fig 77) (*Left*) Right side of pelvis and femur Anteroposterior view The bones are denser than normal but involvement is patchy rather than in a solid fashion as occurs in the severest examples. Lateral femoral bowing is conspicuous. Compare with Figures 207 and 208 (*Center*) Left side of pelvis and femur Anteroposterior view The findings are similar to those of the opposite side. In severe cases, there is often clubbing of the distal femur (*Right*) Both legs, Lateral view Bilateral anterior tibial bowing is present. Irregular transverse lines of increased density are seen in the medullary cavity of both tibiae.

ever it is a true developmental disease. Many theories have been offered to explain the fundamental nature of the disease but none is completely satisfactory.

The various theories regarding the etiology of osteopetrosis include those of parathyroid dysfunction, polyglandular dysfunction, chronic bone infections, disturbance of calcium metabolism and poisoning with phosphorus or fluoride. The disease is believed to be caused by faulty reabsorption of cartilaginous ground substance and of newly formed bone.⁸⁻¹¹ Direct inheritance from an affected parent either from the mother¹² or from the father¹² has been described.

Kelley and Lawlah¹⁴ reported 4 examples of the disease in a third generation of a family they presented.

Variations. There are variations in the manifestations of this disease. However, on analysis the differences appear to be only in degree—a part or all of the skeleton may be involved. Furthermore, the involved portions may vary in the amount of change.

Some workers believe the disease is always present at birth, is generalized and affects all bones equally.¹⁴

Clinical Features. These may be divided into two phases. The first has to do with the appearance of the patient. The second deals with the specific changes in the skeleton with its secondary complications.

These patients demonstrate delayed development—even dwarfism. Other clinical findings are observed that result from either bony change or blood disturbances.

1 Impingement on the cranial foramina because of failure of modeling of the skull may result in (a) optic atrophy (b) deafness (c) hydrocephalus (d) nystagmus (e) ocular palsy and (f) facial palsy.

2 Fractures, usually of transverse pathologic type because of poor bone trabeculation and abnormal matrix modeling.

3 Deformity, even of long bones with shortened shafts and widened ends resulting from faulty modeling.

4 Osteomyelitis particularly in the jaw.

resulting from teeth that are often late in erupting. These teeth are defective in quality and they decay. Dental caries combined with compression of the nutrient foramina of the jaw results in mandibular necrosis and spread of infection.

5 Myelophthistic anemia which occurs from bony obliteration of the marrow cavity including the hematopoietic areas of the flat bones. This will result in the typical picture of a secondary anemia which will not respond to any hematopoietic stimulant. There is extramedullary hematopoiesis with enlargement of the liver, the spleen and the lymph nodes.

LABORATORY DATA. Metabolic studies have shown normal levels in the blood for calcium, phosphorus, magnesium and phosphatase.

Detailed hematologic examination may provide suggestive data. Progressive anemia with a falling white blood-cell count and decline of platelets indicates that death is imminent. In the early condition the color index is low.

(Puncture of the bones to examine the marrow is rather difficult because of the density of the cortex.)

There are signs of extramedullary blood formation such as splenic and hepatic enlargement and immature cell forms in the peripheral blood.

Van den Bergh test is sometimes indirect positive.

Chemical analysis of bone ash shows the same calcium-phosphorus content as in normal bones. The calcium in the separate Haversian osteones is not increased. In fact a lime-structure examination reveals that there is exactly the same amount of calcium in marble bones as in normal bones laid down as hydroxyl apatite (Bodansky).

ROENTGENOGRAPHIC APPEARANCE. The only feature common to all of the reported cases is the roentgenographic observation of increased density with loss of detail of almost all skeletal bones.^{2, 10}

Prenatal Roentgenographic Features. The prenatal roentgenographic features are: (a)

increased and generalized density of the bones (b) widening and fine mottling of all the long bones especially the tibiae and the ulnae (c) narrowed medullary cavity, (d) thickening of the cortex (e) absence of periosteal thickening (f) base of the skull exceedingly dense (g) sella turcica flat (h) increased striae in parietal, frontal and occipital bones (i) calcification of kidneys and (j) no periosteal thickening.

All the bones of the skeletal system are involved. The vertebrae, the pelvic bones, the base of the skull and the ends of the long bones are affected most extensively. The base of the skull is frequently the site of the lesion and the foramina of exit for the cranial nerves are narrowed. In consequence there is pressure on the cranial nerves with sequelae, e.g., facial paralysis or palsy, speech defects, deafness and optic atrophy.

The hard cortical bone is more than twice the usual thickness and condensation and broadening of the osseous trabeculae are present. The spongiosa and the marrow elements may be largely obliterated by the encroaching compacta and replaced by fibrous tissue. The hyperplastic bone growth is endosteal in its entirety.

The ossification centers as previously stated appear at the normal time.

Postnatal Roentgenographic Features. In children the lesions are first noted at the ends of the long bones, particularly in the lower end of the femur and the upper end of the humerus, or in the periphery of the partly ossified tarsals and carpals, the vertebral bodies and the pelvic bones.

Complete marbling of the bones does not occur until after puberty.

The condition starts at the ends of the diaphyses and passes toward the mid-area of the shaft. In the early stages it appears as a dense band similar to that seen in lead poisoning.

The aforesaid changes are generalized as a rule, although often the humeri and the bones of the lower arm and the mandible are less affected than those of other skeletal

parts. The greatest increase in density is found in the skull the vertebral bodies the pelvis, the upper third of the femora and the lower third of the tibiae and the fibulae (Areas of osteoporosis have been reported)

The concurrence of osteomyelitis is not uncommon especially in the mandible the maxillae the femora and the scapulae. Sometimes rickets is an associated disease

Fractures are found especially indications of old ones Obviously, variable degrees of deformity may be seen in consequence of the fractures

Pathology.¹⁴ **GROSS APPEARANCE.** The osseous changes are notable in the gross appearance and the physical properties of the bone The bones are heavy thick and hard to touch. There is a tendency to fracture rather than to bend The long bones in the well-developed condition are clubbed or hourglass-shaped with the most extensive clubbing at the ends Clubbing is usually symmetric and equal The cut aspect reveals a thickened compacta and a spongiosa of finely meshed trabecular composition with little or no observable marrow cavity

The membranous bones (e.g., the vault of the skull) reveal densely arranged trabeculae of spongy bone which is devoid of diploic structure. There may be fibrous aplasia of the hematopoietic tissues in bone liver spleen and kidneys

MICROSCOPIC APPEARANCE. The pathologic changes in congenital marble bones consist primarily of a disturbance of ossification—an increase in the cortical bone to perhaps twice its normal density The growth takes place entirely from the endosteum with as aforesaid a crowding of the marrow cavity (often with complete obliteration) and of the spongiosa or with replacement by fibrous tissue

Various osseous alterations are constant while others depend mainly on the degree of development or the rate of progress of the disease Growth in length and diameter is slightly retarded Expansion and clubbing of the ends of the long bones (especially of the femora) are characteristic. But, with

few exceptions there is no periosteal involvement Centers of ossification about the normal time and the unions are but little delayed.

The increased density advances diaphyses and becomes homogeneous for the bands and the striations parallel the epiphyseal lines *These all bands of increased and decreased are pathognomonic of osteopetrosis*

The line of fracture is characteristic at right angles to the shaft and coincides with the transverse bands of lessened density

Cranial changes are more extensively pronounced in the basal part Ossification of the sutures is retarded and hyaline changes have been reported. A sella turcica may encroach on the optic gland and result in disturbances of vision Pressure on the optic nerves causing atrophy of the optic foramina, may lead to primary optic atrophy

Concurrent bone sarcoma occurs has been reported

Diagnosis. The signs of the disease are characteristic that there is no difficulty in making the diagnosis The disease may be associated with others as in the case of Hodgkin's disease reported by Stein.²⁰

The condition most commonly observed is when patients are born with apparent rickets necrosis of jaw bone severe anemia or failing sight Retarded growth is common and is more pronounced in those examples in which the disease is fully established early in life

The diagnosis rests on the radiographic appearance of osseous sclerosis which is denser symmetric and more widespread than in any other skeletal condition.

The contour of the long bones may be expanded but nevertheless remain normal Where the osseous sclerosis makes its appearance first at the ends of the long bones and progresses toward the mid shaft, the diagnosis is clear but if the site is unusual roentgenographic

ances may be confused with that of osteogenesis imperfecta tarda

On account of the frequent association of hydrocephalus and striking bossing of the skull bones the head assumes a characteristic appearance. The veins in the scalp are dilated. The closing of the anterior fontanel is usually much delayed.

The teeth are often late in erupting and defective in quality and they decay early.

Differential Diagnosis. The fully developed syndrome consisting of pathologic bones retarded development, optic atrophy, anemia and enlargement of lymphoid tissues is not confused easily with any other disease.

In attempts to arrive at a final diagnosis it is well to keep other osseous lesions in mind where there is increased density of bone. For example (1) lines of arrested growth (2) osteitis deformans (3) inflammatory sclerosis (4) fibrous dysplasia of bone (5) melorheostosis or Léri variety of marble bones, (6) osteopolkilosis (7) leontias osseum (8) neurofibromatosis (9) osteogenic sarcoma (10) increased density caused by prolonged ingestion of fluorides and (11) metastatic infiltration secondary to prostatic cancer.

Differentiate osteopetrosis from

Myelosclerosis. This occurs later in life there are no spontaneous fractures and no characteristic roentgenographic appearances.

CONDENSING OSTEITIS (SICARD) This is characterized clinically by localized lumbocrural sciatic pain. It sometimes is associated with a neuritic variety of muscular atrophy. Roentgenographically there is an increased density of bones of the lumbar part of the spine and the pelvis without contour alteration of the involved parts. The condensation may appear in foci which are separate or contiguous and which fade gradually in the contiguous normal bone. Constitutional and hemorrhagic changes are absent.

IBORYING OSTEITIS (PUTTI) This is characterized by the ivorylike density of a

single bone usually in an extremity. There is some predilection for the area of the nutrient artery. No constitutional disturbances are found.

IVORY VERTEBRAE. These may be found in Paget's disease or metastatic prostatic cancer.

MELORHEOSTOSIS (LÉRI) Roentgenographically melorheostosis shows increased density and contour distortion of one or more bones in an extremity. When the disease involves more than one bone it invades the joints between producing characteristic changes therein. Roentgenograms of the bones simulate the appearance of opaque wax heated to the melting point and flowing down the side of the bone (Figs 83 to 90). It is not a generalized disease from a roentgenographic viewpoint.

CHRONIC METALLIC POISONING. Poisoning with lead or phosphorus may cause indecision regarding the diagnosis. The history, the chemical analysis and the examination of the red blood cells are obviously of great significance. Osteopetrosis presents no peripheral neurologic features in contradistinction to chronic lead poisoning.

Chronic fluorine poisoning presents changes which may be mistaken for osteopetrosis. The history is of great importance. In fluorine poisoning, the osseous pattern remains unaltered and calcium fluoride crystals are identifiable in the haversian canals. The adjacent soft tissues show osteophyte formation with calcification of the intervertebral ligaments and the periosteal deposits.

CEROLITE DUST POISONING There is systemic involvement because of fluorine which converts the bone crystal to a fluorapatite. The pathologic process consists in a diffuse osteosclerosis where the pathologic formation of bone starts in both the periosteum and the endosteum. The compacta increases in density. The medullary cavity decreases in diameter. There is extraordinary new bone formation from the periosteum. Ligaments that normally do not calcify or only in advanced age undergo a great degree of

calcification. Signs of bone destruction are absent.

VITAMIN D POISONING Dense bands are formed across the metaphyses.

LEUKEMIA In leukemia, there develops diffuse osseous sclerosis such as was first described by Hueck²¹ and others. *The leukemic changes are primarily infiltrative and therefore destructive.* It usually involves the periosteum. Sclerosis when present, is not so generalized. Roentgenographic shadows are less opaque than in osteopetrosis and the characteristic epiphyseal stratification with obliteration of the bone structure is absent (Figs. 376 and 377).

OSTEOGENESIS IMPERFECTA. When multiple fractures take place the differential diagnosis between osteopetrosis and osteogenesis imperfecta is frequently not a simple matter. In the latter condition however the density of the bones is *decreased* rather than increased and trabeculae are present. In addition pronounced deformi-

ties and bowing of the bones caused by softening are seen (Figs. 19 to 28).

PAGET'S DISEASE OF BONE. This disease also may present a difficult diagnostic problem in older patients. The changes in the skull the pelvis and the long bones of the extremities are however, usually characteristic. The bones are not homogeneous and the trabeculae instead of being absent, are prominent and thickened (Figs. 262 to 320).

CONGENITAL SYPHILIS This is often a confusing diagnostic problem. There are not only great periosteal thickening and sclerosis of the bone proper but also tracts of destruction in the metaphyseal area. The bones of the base of the skull usually involved in osteopetrosis are rarely so in syphilis. Serologic studies are of course of importance in the differential diagnosis.

CAMURATI ENGELMANN DISEASE. A variable degree of homogeneity is noted in the roentgenograms. There is usually fusiform thickening of the cortical layer of the long



FIG. 80 Osteopoikilosis (From Dr. M. M. Pomeranz) Pelvis. Diffuse changes in the upper femora and in the pelvis especially the pubic and ischial rami. Multiple bone islands are actual zones of compact bone within the cancellous structure.



FIG. 81 Osteopoikilosis. (From Dr M. M. Pomeranz) Shoulder. Bone islands are seen in the glenoid and in the neck of the scapula as well as in the head and the neck of the humerus.



FIG. 82 Osteopoikilosis. (From Dr M. M. Pomeranz) Forearm and wrist. Changes are evident in the distal radius and ulna, the carpal bones, the metacarpals, and to a lesser degree in the phalanges.

—and sometimes of the short—tubular bones without clear structural mutation. The periosteum appears to be unaffected. The marrow cavity remains patent but is slightly narrowed by the widening compacta. The epiphyses and the metaphyses remain uninvolved.

Treatment. Osteopetrosis is incurable.

Prognosis. The prognosis is favorable except that the early infantile examples of the condition terminate in death from anemia.

OSTEOPOIKILOSIS

(Syn. Osteopathia condensans disseminata; osteopocilia; Albers-Schönberg disease; familial disseminated osteosclerosis; spotted bones (Gr.); osteitis condensans disseminata.)

Definition. Osteopoikilosis is an uncommon affection in which multiple islands of compact cancellous osseous tissue are found especially in the pelvis and the long bones (Figs. 80 to 82).

Historical Notes. The first description was by Stieda.¹ A more complete account was given in 1915 by Albers-Schönberg.² Although osteopoikilosis bears no obvious relationship to osteopetrosis, sometimes it is erroneously termed Albers-Schönberg disease. The term osteopoikilosis is derived from the word *osteopocilia*, first used by Ledoux, Chabanaix and Dessane.³ Osteopathia condensans disseminata was suggested by Wachtel.⁴

Incidence. The condition is congenital and may be familial and hereditary. Most of the reported cases were discovered during adulthood in both sexes.

Etiology. The etiology of the disease is unknown. It has been noted in three generations (Buschke,⁵ Henson⁶). Males are affected more than twice as commonly as females. All ages from fetal life to the sixth decade have been reported as affected. Some clinicians believe the condition to be always congenital.

Clinical Features: **PHYSICAL—SIGNS AND SYMPTOMS.** The lesion is asymptomatic. It is usually discovered accidentally.



FIG 83 (*Left*) Melorheostosis. (Figs. 83 to 87 from Dr. M. M. Pomerans) White female 27 years old. Lower pelvis and left femur. Anteroposterior view. Showing the general distribution of the flowing hyperostosis.



FIG 84 (*Right*) Melorheostosis. (Same patient as Fig. 83) Lower femur and upper tibia. Anteroposterior view. Marked hyperostotic changes are seen within the shafts but are present also upon the surface of the bones.

tients are examined roentgenographically for some other condition (Figs. 80 to 82). There are no spontaneous fractures.

Concurrent skin lesions termed dermatofibrosis lenticularis disseminata have been described with or without keloid formation.⁷

CHEMICAL DATA. Blood examinations are negative. There are no disturbances of mineral metabolism.

ROENTGENOGRAPHIC EXAMINATION. Roentgenographically, round or oval areas of condensation are seen scattered throughout the spongiosa of the involved bones and linear streaking along the shaft. The spots vary in size between 2 and 10 mm.

At the epiphyseal and the metaphyseal

portions of the long bones the areas are roughly circular but, where they extend into the diaphysis the opacities become oval or striate. In the short bones of the hands and the feet, shafts and epiphyses are spotted (Fig. 82).

In the ilium, the spots usually are found near the acetabulum, the sacro-iliac joint and the crest, leaving the central part of the bone unaffected (Fig. 80).

Clavicular involvement is mild and at the outer third. In the scapula, the acromion is the common site. All bones may be involved, but in the usual case the ribs, the skull and

FIG. 85 Melorheostosis (Same patient as Fig. 83) Lower femur and upper tibia. Lateral view. Showing similar flowing hyperostotic changes.

the vertebral column are involved only slightly.

Pathology: GROSS APPEARANCE. Multiple foci of compact or dense cancellous bone with irregular and sometimes notched borders are found in the middle of the normal cancellous bone. The ends of the long bones are commonly involved. Conglomeration is actually an overlapping of small lesions to form a single large island.

MICROSCOPIC APPEARANCE. The predominating picture is that of condensed cancellous bone not cortical bone. The dense spots scattered through the bone are found to consist of many regularly arranged trabeculae. These are of different thickness but are usually denser than normal. Generally they are arranged in the axis of the bone. At the



FIG. 86 Melorheostosis (Same patient as Fig. 83) Lower tibiae and ankles. Anteroposterior views. Changes are present on the left side only and are seen in the tibia and the talus.

periphery the spots merge into the circumjacent cancellous bone. They have no connection with epiphyseal cartilage. There is no sign of fibrosis of marrow. In advanced conditions the foci are of great density and commonly occur at the areas where traction and pressure lines cross. The surrounding spongiosa often appears atrophic. The spots involve the spongiosa and spare the cortex.

Diagnosis and Differential Diagnosis. The advanced condition is easily differentiated roentgenographically from other diseases of the skeletal system.

MELORHEOSTOSIS. The lesions in long bone ends are more varied in shape and size and are in a sense blotches rather than accumulations of small islands of bone (Figs

83-86, 88 to 90). The candlewaxlike bands of dense bone in the shafts of the long bones clinch the diagnosis (Figs 84 to 86). In melorheostosis a short bone may contain a large single patch of dense bone, further more in the Léry type dense spots may be seen in the soft tissues, a condition never found in osteopoikilosis (Fig 87).

MULTIPLE ENCHONDROMATOSIS. Although calcification and ossification may be found in the cartilage masses seen in this disorder the lesions can be easily differentiated. In osteopoikilosis the bones are "peppered" with compact osseous spots, whereas in dyschondroplasia, the basic cartilage architecture will be recognizable (Figs. 53 to 59).

SERAMOID AND ACCESSORY BONES. These



FIG. 87. Melorheostosis. (Same patient as Fig. 83.) Both feet. Oblique views. Showing that changes are predominant in the left talus.

also must be borne in mind in the differential diagnosis.

OTHER SKELETAL CONDITIONS The spotted appearance of osteopoikilosis makes it easy to differentiate from the osseous density of localized osteosclerosis caused by tuberculosis syphilis osteomyelitis osteoplastic carcinoma etc. In marble bones and in Paget's disease of bone the osteosclerosis is more diffuse.

Treatment The condition does not require medical or surgical treatment.

MELORHEOSTOSIS

(Syn Léri variety of osteopetrosis osteosis eburnacea monomelica—Putti ostosis eburnosa monomelica osteosis eburneans monomelica osteopathia hyperostica flowing hyperostosis.)

Definition. As a rule melorheostosis is a bizarre irregular flowing hyperplastic deposit upon and in the bones of one extremity. By definition it means "member flow."

Historical Notes. Léri and Joanny¹ published a report regarding the first case in which an arm was affected. They suggested the descriptive title melorheostosis which is now widely used. The distribution of dense areas suggested to them the flow of tallow along the sides of a burning candle.

Incidence. Both sexes are affected the incidence being higher in males. The disease is not hereditary. It has been reported from childhood to past middle life.

Etiology. The cause of the disease is unknown. It is probably a mesenchymal defect.² It usually involves a single limb a so-called monomelic distribution (Figs. 83 to 87). The lower extremities are involved



FIG. 88 Melorheostosis. White female 13 years old. Pelvis and upper femora. Anteroposterior view. Note the creeping substitution and the flowing hyperostosis in the left ilium and the left proximal femur.

periphery the spots merge into the circumjacent cancellous bone. They have no connection with epiphyseal cartilage. There is no sign of fibrosis of marrow. In advanced conditions the foci are of great density and commonly occur at the areas where traction and pressure lines cross. The surrounding spongiosa often appears atrophic. The spots involve the spongiosa and spare the cortex.

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FIG. 89 Melorheostosis. (Same patient as Fig. 88.) The frog leg lateral position of the femora shows ossification immediately contiguous to the left lesser trochanter as well as the other findings of Figure 88.



FIG. 90 Melorheostosis. (Same patient as Fig. 88.) Left knee. Anteroposterior view. Condensation is seen within the lateral femoral condyle. Note the growth disturbance producing genu valgum.

more commonly than the upper. Fairbank has reported cases in which the limb involvement is multiple.³

Clinical Characteristics. From analysis of the disease, it can be deduced that the clinical picture could be correlated with the characteristic pathologic findings.

Pain can and does occur in association with progressive new bone formation. Paresthesia, hypoesthesia and actual atrophy may occur as a result of nerve pressure.

Growth disturbances such as bowleg, knock knee or even shortening may occur because of epiphyseal blocking on one side or total epiphyseal arrest (Fig. 90). Findings associated with overgrowth and deformity from bone thickening have also been noted. Since this process crosses joints and involves periarticular soft tissues limitation of joint motion may occur. Also a picture similar to that of scleroderma with fibrosis of muscles has been described.⁴

Other clinical features may be swelling of the limb edema and induration Erythema of the skin over the affected parts of a hand has been reported Nodular induration of the tissues may be present Occasionally there is irregular thickening of a bone which may be felt easily particularly when the phalanges are affected Diminished sensibility and tingling have been noted

The outline of a limb is finally distorted Shortening of the limb has been a feature in some patients while less frequently the affected one has been longer than its fellow

Deformities caused by bone thickening associated with limited movement of one or more digits of the hand is not uncommon when the upper limb is involved

Atrophy from disuse or nerve pressure may be present

Pes valgus genu valgum curvature of a bone and enlargement of a knee have all been reported (Fig. 90)

CLINICAL DATA Blood examination reveals nothing of importance.

ROENTGENOGRAPHIC FEATURES Roentgenographically melorheostosis is characterized by long broad streaks of calcific density which extend lengthwise along the affected bone (Figs 83 to 90) As a rule the streaks are seen in the axis of the bone however they may reach the compacta along the inner or the outer aspect

Pathology: Gross Appearance. There are no reported postmortem studies Therefore the general appearance of the bone itself can only be postulated from x-ray studies

Microscopic Examination. Most reports indicate that dense areas are the seat of sclerosis with compact overcrowding of lamellae arranged in a curious manner there is an interlacing pattern of immature and adult bone Concentric perivascular ossification is sometimes mentioned.

The pathologic examination of the affected area discloses a bony substance which as previously mentioned resembles compacta. This is caused by greatly increased formation of osteoblasts and dimin-

ished formation of osteoclasts In consequence the haversian and the Volkmann canals become walled up There are no signs of inflammation

Diagnosis. As a rule the diagnosis is made easily The only characteristic feature is the bizarre appearance of the bone exemplified by irregular dense deposits of bone extending lengthwise usually along one side of the bone The outline of the bone is roughened

Differential Diagnosis. Some of the osseous diseases which may require differentiation from melorheostosis are

CHRONIC PYOGENIC OSTEOMYELITIS In this condition the history and the presence of sequestrum related to the involucrum make the diagnosis

PAGET'S DISEASE. In this condition the involvement is usually in later years and may be multiple The skull and the spine commonly are involved. The entire bone not only a side shows enlargement (Figs 262 to 320)

LUETIC OSTELITIS Acquired syphilis may take the form of a chronic diffuse or localized periostitis or a diffuse or gummatous (localized) osteitis It is recognizable by the characteristic nocturnal pains in the limbs. There is usually a positive Kahn or Wassermann test. Hereditary syphilis may reveal the same lesions In infancy aside from the usual stigmas as a rule chronic non-suppurative osteochondritis (chronic metaphysitis) is present. The physiognomy is characteristic the bosses on the frontal and the parietal bones Parrot's nodes the saddle nose and Hutchinson's teeth.

OSTEOPETROSIS In generalized osteopetrosis every bone is affected to some extent and the distribution of the density in separate bones differs greatly from that seen in melorheostosis (Figs 77 to 79)

OSTEOPORIKILOSIS. From osteoporikilosis, the differentiation is also easy provided that the whole roentgenographic picture is closely scanned and that undue attention is not paid to the appearance of one or two epiphyses (Figs. 80 to 82) Osteoporikilosis is a general affection of the skeleton and it is not con-



FIG 91 Neuroilemmoma of ilium. (From Dr M M Pomeranz) A multiloculated area is present in the wing of the ilium. Biopsy indicated neuroilemmoma

finied to one limb as melorheostosis usually is moreover it is never associated with opacities in the soft tissues

POLYOSTOTIC FIBROUS DYSPLASIA. This disease may simulate melorheostosis particularly when it is unilateral. The shaft of a bone in Albright's syndrome occasionally may show marked density and no cystic change

However in this condition numerous bones are involved and some will inevitably show the characteristic cystic lesions (Figs. 29 to 39). Furthermore there may be other chemical findings such as sexual precocity and skin lesions which occur in the Albright syndrome

OSTEOBLASTIC CANCER METASTASES The primary focus is usually discoverable particularly cancer of the prostate. This usu-



FIG 92 Neurofibromatosis (From Dr M M Pomeranz) Severe rotatory lateral curvature of the dorsal spine associated with neurofibromatosis. No neurofibromata have been found in the vertebrae of these cases.

ally is associated with changes in the spine as well as in the pelvis and other areas (Figs. 363 to 365). As in the case of most metastatic bone lesions usually it does not go below the knees or the elbows. Phosphatase alkaline and acid are also elevated

CALCINOSIS. The deposition of lime salts usually is not connected with the bone. It is less dense and usually is deposited secondarily

Treatment. As a rule no treatment is necessary

Prognosis. Melorheostosis is a slow progressive disease with no tendency to malignancy. There may be an increased weakness from secondary disturbances of the nerves and increased disability if there is interference with joint function.

NEUROFIBROMATOSIS

(Syn. Fibroma molluscum, neurinoma, tosis, von Recklinghausen's disease, multiple neurofibromatosis)

Definition. Neurofibromatosis is a congenital dysplasia manifested by developmental changes in the nervous system

cutaneous spots and fibromas and multiple neurofibromas of the cranial and the peripheral nerves. Some cases show bone and joint changes (Figs 92 to 95)

Historical Notes. In 1849 Smith¹ described the disease in detail but failed to recognize the nerve sheath origin of the multiple tumors. According to Ewing² Kolliker in 1860 was the first to describe neurofibromatosis. Thomson³ described its hereditary nature. The hereditary nature of

FIG 93 Neurofibromatosis. Negro male 14 years old. Dorsolumbar spine. Anteroposterior view. Right dorsal left lumbar scoliosis associated with "café au lait" spots. Note the sharp wedging of the concave aspect of the bodies of the fourth and the fifth thoracic vertebrae. The peculiar shape of the lumbar transverse processes is shown better in Figure 94.



FIG 94 Neurofibromatosis. (Same patient as Fig. 93) Lumbar spine. Anteroposterior and lateral views. Note the concave indentations on the anterior aspect of the upper three lumbar vertebral bodies in the lateral x ray picture. The elongated transverse lumbar processes on the right side are thrown into profile by the rotatory deformity.

neurofibromatosis was established conclusively by Preiser and Davenport.⁴

In 1921 Weiss² first described the high incidence of scoliosis in neurofibromatosis. Stahnke⁵ was the first to suggest that the condition was a systemic one. Brooks and Lehman⁷ were the first to emphasize the abnormalities of growth and to note subperiosteal bone cysts which were felt to result from tumor tissue growth.

The French clinicians Marie Bernard and Chauffard called attention to the cutaneous pigmentary anomalies in neurofibromatosis while the visceral and the bone changes were early reported in the German⁸ the English and the American literature.

In 1882 von Recklinghausen⁹ published his classic monograph. This clearly defined neurofibromatosis and correlated the skin

and the subcutaneous nodules with the course of peripheral nerves. He considered that these nodules arose because of some derangement of the peripheral nerve endings. His name has since become identified with this condition. It should be emphasized that neurofibromatosis is a different entity from the other disorder that bears his name which is hyperparathyroidism or osteitis fibrosa generalisata.

In 1937 Ducroquet¹⁰ reported the occurrence of congenital pseudarthrosis of the tibia in neurofibromatosis. Barber¹¹ confirmed this finding.

In 1941, Moore¹² described hypertrophy underdevelopment growth distortions in the vertebrae and pseudarthrosis after fracture of the tibia in this entity. He found peripheral neurofibromas in these cases. He con-



FIG. 95 Neurofibromatosis. (Same patient as Fig. 93, 16 years old.) Left ankle, lateral view. Left calcaneus, axial view. Left-sided spastic flatfoot was noted 2 years later in this patient. Talocalcaneal lippling is seen in the lateral ankle x-ray picture. The special axial view of the calcaneus demonstrates the bony bar partially obliterating the inner aspect of the joint between the sustentaculum and the talus.

cluded therefore that there was a relationship between neurofibromatosis and the aforementioned skeletal changes.

Green and Rudo¹³ reported a case in which they had found an intra-osseous neurofibroma.

McCarroll¹⁴ pointed out and confirmed the presence of pathologic findings of neurofibromatosis at the same sites as soft tissue hypertrophy, lymphatic involvement and vascular changes. Cases of pseudarthrosis of the tibia and scoliosis had neurofibromas elsewhere but not at the site of the osseous disturbance. To the skeletal changes associated with this entity, McCarroll also added spondylolisthesis and melorheostosis. Almost all of his cases presented "café au lait" spots.

Aegerter¹⁵ was not satisfied that a neurilemmoma of the tibia could cause the classical picture of congenital pseudarthrosis. He felt that it was hard to explain a bone defect on the basis of a lesion of neuro-epithelial origin. Moreover, in his cases the pathologic findings at the site of the pseudarthrosis of the tibia were not consistent with neurilemmomas. He concluded that both the neurofibromatosis and the pseudarthrosis were on the basis of an underlying combined ectodermal and mesenchymal defect.

Incidence. The disease has been estimated as occurring in about one out of two thousand persons according to Preiser and Davenport.⁴ Castellino¹⁶ wrote that "the disease assumes a familial character and may be transmitted to the first, second or third generations." Gardner and Turner¹⁷ described the abnormality in six generations. Garland¹⁸ wrote of four brothers who showed signs of the disease.

The disease is seen in all ages, especially among males.

Etiology. It is widely agreed that heredity plays an essential part in the development of neurofibromatosis. Turner and Gardner¹⁹ believed that there was involvement of all the sheaths and enveloping membranes of the nervous system.

The actual cause is unknown.

Clinical Characteristics: PHYSICAL. There are four types of skin lesions.

1 "Café au lait" spots with smooth rounded margins. This is primarily a pigmentation and not a tumor formation. It has been described by Albright as "coast of California type" in contrast with the irregular margins of the skin lesions of Albright's syndrome in fibrous dysplasia. This latter he terms "coast of Maine." These spots vary in size from 2 mm. to as much as 5 cm. in diameter. This pigmentation may be present at birth or develop later.

2 A verrucous or villous type of skin hypertrophy described originally by Weiss.² This type is associated with extremity hypertrophy due to increase in size of both the soft tissue and the bony structures.

3 The so-called neurofibroma or fibroma molluscum is the form originally described by von Recklinghausen. This is a tumor possibly originating from the Schwann cell. For that reason it is referred to by some as a neurilemmoma. Other workers, however, believe the origin to be fibroblastic; hence the term neurofibroma or fibroma.

The histology of these lesions has been very difficult and the question of mesodermal versus ectodermal origin is not yet settled.¹⁵ It is possible that tissue culture may help to solve this problem.

These nodules vary in number, size and shape. They may occur literally by the hundreds to cover the entire body; conversely they may be few in number. The size may vary from a tenth of an inch in diameter to several inches in diameter. They may be sessile or pedunculated.

4 Marked general hypertrophy of the skin and the subcutaneous tissues is an elephantiasislike manifestation of this syndrome. This process may involve only a part of an extremity as a finger or it may involve an entire extremity. There is generally an associated skeletal hypertrophy in association with this skin manifestation.

There are several major phases of skele-

tal manifestations. The first is scoliosis. This has been referred to in earlier literature.⁸ The scoliosis is frequently a kyphoscoliosis. Its most common location is the lower dorsal region. It may occur elsewhere. The classical case presents a sharp angular curve with vertebral wedging and atypical compensatory curves that actually do not compensate (Fig. 92).

These curves are noted for rapid progression and the complication of paraplegia which is rare in the idiopathic type.

Other bone changes include bowing of the tibia, aptly termed congenital kyphoscoliosis of the tibia by Badgley.²⁰ Fracture is quite common in this anteromedial type of bow and pseudarthrosis a frequent sequel to the fracture.

In addition, there may be retardation or increased rate of bone growth. This may involve a single bone or an entire extremity. Overgrowth of soft tissue accompanies bone hypertrophy.

The subperiosteal cysts of course are not apt to be found on clinical examination.

Asymmetry of the skeleton is a part of the hypertrophy or retardation of bone development, but there also may be actual absence of portions of the skeleton.

Of interest are two additional skeletal abnormalities reported by McCarroll.¹⁴ These are spondylolisthesis and melorheostosis.

Nerve tumors have been found to involve the brain, the cranial nerves, the spinal cord and the peripheral nerves. These may give symptoms related to their location, varying from tenderness of a superficial nodule to paralysis resulting from a central or cord lesion.

Endocrine changes occasionally are associated with multiple neurofibromatosis. Menstrual abnormalities, acromegaly, cretinism, delayed or incomplete sexual development, myxedema, tetany, Addison's disease, hyperparathyroidism and a diabetic blood-sugar curve.²¹

CHEMICAL FINDINGS. No diagnostic laboratory changes are found in this condition.

X-RAY FEATURES. Changes include specific findings secondary to invasion by or pressure from neurofibromatous tissues.

There may be bone cysts located superficially centrally in the cortex and rarely in the endosteum (Fig. 91).

Sometimes these cystic changes are associated with sclerosis. This sclerosis may be of the periphery of a cyst or appear independently contiguous to a soft tissue neurofibroma.

In the hyperplastic group there may be local gigantism, especially of the acral portions.

Disorders of bone growth in the order of hypoplasia and hyperplasia may be noted. In the instance of hyperplasia and occasionally of hypoplasia also there is associated skin and other soft tissue change.

The bones of the skull often are involved. Erosion of circumscribed areas, odd vascular designs and enlargement of the sella, the orbit and the optic canal have been noted. Gross asymmetries, absences of portions of the skull and areas of increased density have been noted.

Erosion of the petrous portion of the temporal bone often is observed in association with a neuroma of the eighth cranial nerve.

The spine frequently shows a kyphoscoliosis. This deformity is sharply outlined and rapid in development. It does not tend to strike a balance in alignment through adequate compensating curves, as frequently is the case in idiopathic scoliosis. The wedging of the vertebra at the apex of the curve is severe in neurofibroma. At times, this may lead to the erroneous diagnosis of hemivertebra. In neurofibromatosis serial films will show progression of the curve thereby demonstrating progressive wedging of the apical vertebra (Figs. 92 to 94).

Bowing deformities of the tibia are usually at the junction of the middle and the lower thirds. They are usually anterior or anterolateral. Frequently they are associated with an equinovarus deformity of the foot. A less common type is the postero-

medial type of bow associated with a calcaneus or calcaneovalgus foot deformity.

Badgley²⁰ has emphasized a characteristic dense bony mass found roentgenographically on the concave side of the curve. This frequently is associated with obliteration of the marrow cavity. Moreover the bone trabeculations in this dense mass radiate from the apex of the curve rather than remain in the longitudinal axis.

Serial radiograms have confirmed the fact that the posteromedial and the posterior types frequently correct spontaneously. It is true however that these cases of posterior and posteromedial bow had "café au lait" spots in some instances, but were not necessarily true cases of neurofibromatosis.

Moore²¹ has used the term prepseudarthrosis to indicate the stage when roentgenographic findings include severe bowing, narrowing of the bone at the apex of the curve and obliteration of the marrow cavity.

This stage is followed by pathologic fracture and the development usually of a frank pseudarthrosis.

Pathology: GROSS APPEARANCE. These soft tissue lesions of the skin and subcutaneous lesions are self-evident from the clinical description noted above. Their color may be that of the overlying skin or it may be pink or blue. They may be extensions of the small cutaneous nerves.

Neurofibromas also are found in various places in the nervous system—this may include the parenchyma of the brain, the brain stem or the spinal cord. They are also found along the course of the cranial and the spinal nerves where they constitute nodular thickenings of various sizes.

The hypertrophied extremities so-called elephantiasis usually show lymphatic obstruction, fibrosis and occasionally plexiform neuromas. These latter represent wormlike collections of overgrown nerve tissue. Sometimes they may be palpated as they lie just beneath the skin.

Bone changes may be grouped into those due to direct pressure from neurofibromas and those of structural type.

The former include pressure erosions. These result from periosteal or endosteal neurofibromas or rare intra-osseous lesions. They cause thinning of bone adjacent to the lesions. Frequently asymmetry may result especially in the calvarium because these tumors usually occur unilaterally.

Other skeletal changes appear to be related to a mesenchymal defect and usually show no evidence of actual neurofibromatous tissue (Figs. 92 to 95).

Hypertrophy and overgrowth of bones of an extremity frequently are observed in association with soft tissue lesions such as elephantiasis and plexiform neuromas.

Atrophy of an extremity is a rarer defect but this too is associated with soft tissue rather than bone change. Occasionally here too subperiosteal bone cysts may be found.

Kyphoscoliosis or congenital bowing of the tibia has been reported to contain an interosseous neurofibroma.¹² Most workers have not found interosseous invasion by neurofibromas in tibial pseudarthrosis. They find only a gradually progressive bowing with a frequent sequel of pathologic fracture and pseudarthrosis. The tibial ends develop a peculiar pointed configuration with obliteration of the marrow cavity as the bowing progresses to fracture and pseudarthrosis.

The kyphoscoliosis involving the spine is sharp and angular with secondary vertebral wedging severe enough to be confused at times with congenital hemivertebra (Fig. 92). To the authors' knowledge no cases of intra-osseous involvement of the spine by neurofibromas have been reported.

It would be of interest to learn whether involvement of nerves contiguous to the deformity is present. Furthermore, has there been muscle imbalance due to variation in innervation to produce an asymmetric pull to cause the curve? Moreover, this curve rapidly advances at times suggesting a paralytic curve.

MICROSCOPIC APPEARANCE. Nerve involvement is attributable largely to the dominant tissue of a nerve sheath—the neuro-ecto-

tal manifestations. The first is scoliosis. This has been referred to in earlier literature.¹⁸ The scoliosis is frequently a kyphoscoliosis. Its most common location is the lower dorsal region. It may occur elsewhere. The classical case presents a sharp angular curve with vertebral wedging and atypical compensatory curves that actually do not compensate (Fig. 92).

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MICROSCOPIC APPEARANCE. Nerve involvement is attributable largely to the dominant tissue of a nerve sheath—the neuro-ect-



FIG. 97 Chondro osteodystrophy (Morquio-Brailsford) (Same patient as Fig. 96) Cervical spine and base of skull. Lateral view. The vertebral bodies appear compressed and deformed. The atlas and the axis are invaginated into the base of the skull. This is an unusual cause of platybasia or convexobasia.

The neurofibromas of peripheral and cranial nerves and those of the parenchyma of the spinal cord and the brain show a larger proportion of tissue believed to be of Schwann cell origin.

The subperiosteal bone lesions present neurofibromatous changes as do lesions eroding the limb bones and the skull.

The fibrous-tissue components of some of these lesions will show secondary hyaline degeneration, cyst formation and hemorrhage.

Complications and Their Treatment. These may be listed as

- 1 Pressure phenomena related to the neurofibromas, both centrally and peripherally.
- 2 Sarcomatous degeneration of neurofibromas occurs not infrequently (5.5% to 12 per cent).²⁴ If possible, block dissection or ablation is indicated.
- 3 Paraplegia secondary to scoliosis. This is alarmingly more frequent in this condition than in paralytic or idiopathic scoliosis. Cobb²⁵ has pointed out the necessity for careful observation of these cases with early



FIG. 98 Chondro osteodystrophy (Morquio-Brailsford) (Same patient as Fig. 96) Dorsolumbar spine. Lateral view. Dorsal kyphosis and lumbar lordosis are increased. Growth deformity is evident with characteristic "slipper" appearance of the vertebral bodies. However, one or two vertebrae show a "tongue" appearance which usually is considered to be more typical of gargoylism or Hurler's syndrome.

spine fusion where rapid progression is noted.

Moreover, laminectomy in instances of paraplegia in the hopes of finding an intraspinal neurofibroma has resulted in further progression of the curve with no improvement of the paraplegia.²⁶ Correction and spine fusion is the treatment of choice.



FIG 99 Chondro osteodystrophy (Morquio-Brailsford) (Same patient as Fig. 96) Right shoulder girdle and upper humerus. There are metaphyseal sclerosis and associated fragmentation of the epiphyseal plate and the epiphyseal center of the humeral head.



FIG 100 Chondro-osteodystrophy (Morquio Brailsford) (Same patient as Fig 96) Right elbow Anteroposterior view Cubitus varus or reversal of the carrying angle has resulted from fragmentation and condensation of the trochlear or the medial condylar epiphysis in particular

4. Pseudarthrosis of the tibia particularly when it is an anterior or an anterolateral bow Manipulation of the bowed tibia is to be avoided. Prepseudarthrosis or definite pseudarthrosis should be treated by early bone grafting. The most consistently good results reported are those of Moore²². Farmer²³ presented a very interesting approach to this problem with success in 3



FIG. 101 Chondro osteodystrophy (Morquio Brailsford) (Same patient as Fig 96.) Both wrists. Anteroposterior view. There are fragmentation and condensation of the carpal centers. At this age, well formed carpal centers are expected. The bases of the metacarpal bones are deformed and tend to be pointed.



FIG 102 Chondro-osteodystrophy (Morquio-Brailsford) (Same patient as Fig. 96) Pelvis including hips and upper femora. There is marked deformation of the capital femoral epiphyses. It is important to appreciate that the sclerotic area proximal to the epiphyseal plate is condensed bone forming the base of the femoral capital epiphysis. Considerable deformity of uncalsified epiphyseal cartilage must be inferred from the abnormal shape of the rest of the hip joint including the acetabular roof



FIG 103 Chondro-osteodystrophy (Morquio-Brailsford) (From Dr M M Pomeranz) Pelvis and hip joints. Young adult. Severe deformity of both hip joints is evidenced by sclerosis, severe joint narrowing and femoral-head flattening

cases. This involves the use of a composite bone and skin pedicle graft

Prognosis. This disease is a neuroectodermal defect which at times appears to occur concomitantly with mesodermal anomalies (Figs. 94 and 95). The relationship to the longevity and the well being of the patient depends upon the location and the extent of these lesions. It is not a reversible condition.

CHONDRO-OSTEODYSTROPHY

Chondro-osteodystrophy Morquio-Brailsford type is a term coined by Brailsford in 1928 and refers to a severe affliction of the entire skeleton. The defect appears to be an abnormality in skeletal ossification.

Historical Notes. Brailsford presented the radiographic anatomy of this condition in 1928. The first publication on this subject was in 1929.¹ Morquio summarized the clinical features and reported upon it in 1929.²

Incidence. This is a rare deformity and although it may be familial it does not appear to be truly hereditary. Both sexes are affected, males slightly more than females.

Etiology. The etiology is not known. Brailsford advances the hypothesis of a "lethal factor" in the parents introducing a state of incompatibility.³

After evaluation of the material Fairbank concludes that the etiology must still be classified as unknown.⁴

Varieties. The unique thing about this



FIG. 104 Chondro-osteodystrophy (Morquio-Brailsford) (From Dr. M. M. Pomeranz) Knee joints. Anteroposterior view. The upper tibial, the upper fibular and the lower femoral epiphyseal zones are broadened transversely and thinned longitudinally. Cupping deformity of the tibial condyles is beginning.

particular condition is that there appears to be no variation; all cases follow a specific pattern.

Clinical Characteristics: PHYSICAL. Brailsford states¹ that this is a disorder that manifests itself within the first 3 years of life. Fairbank indicates that he has not observed it commonly below the age of 4. Usually it is manifested clinically below the age of 10.

The clinical signs and symptoms are on the basis of gross disturbance associated with multiple epiphyseal involvement (Fig. 96). That is characteristic of this disease state. They may be listed as follows:

1 Dorsolumbar kyphosis (Fig. 98). This is due to the anterior wedging of the vertebral bodies.

2 Settling of the cervical spine shortens the neck (Fig. 97). This is again associated with vertebral body wedging.

3 There may be a scoliosis associated

with the kyphosis. As a result of the vertebral collapse in the dorsal region there is an increase in the anterior-posterior diameter of the chest and even a thrusting forward of the sternum.

4 Multiple epiphyseal deformities of the long bones and the joints will result in such changes as genu valgum, coxa vara and pes planus. The over-all gross picture is one in which the individual tends to remain seriously dwarfed in size (Figs. 99 to 108).

5 There is progressive flaccidity of the muscles and marked relaxation of the ligaments. In association with these and a deformity such as coxa vara, dislocations of the hips may occur.

6 Dislocation of the patella is also seen.

7 The hands are deformed in that the fingers appear broadened with swellings of the interphalangeal joints (Figs. 101 and 108).

8 The skull appears relatively normal.



FIG. 105 Chondro-osteodystrophy (Morquio-Brailsford) (From Dr. M. M. Pomeroy). Knee joints. Anteroposterior view. Young adult. To be noted in particular are fragmentation, condensation and deformity of the lateral condyle of the tibia.



FIG 106 Chondro osteodystrophy (Morquio-Brailsford) (From Dr M M Pomeranz) Knee joint. Lateral view Young adult. This view shows fragmentation, condensation and deformation to be present in the femoral condyles and the patella as well



FIG 107 Chondro osteodystrophy (Morquio-Brailsford) (From Dr M M Pomeranz) Lower extremities. Lateral views. Child Very severe typical changes with enlargement, cupping, fragmentation sclerosis and abnormal shape of the epiphyseal centers and the metaphyses. The shafts of the long bones are broadened and foreshortened. The tarsal bones are also affected

but facial features may be unattractive (Fig 96) Intelligence appears to be unimpaired

ROENTGENOGRAPHIC APPEARANCE. Brailsford divides this into early and late manifestations.² In the early stage major changes are found in the vertebral bodies and the epiphyseal ends of long bones. The outlines of the vertebrae show platyspondyly. The tongue-like prolongation of the middle portion of the anterior part of the vertebral body is supposed to be diagnostic (Fig 98). This of course results from the failure of the formation of the upper and the lower epiphyseal plates of the vertebral bodies. A slipper-shaped projection on the inferior surface of some vertebral bodies may be observed in association with the more characteristic central or tongue-like projection

on other vertebrae. This slipper-shaped projection is more apt to be associated with gargoyliism although it can be present also in Morquio-Brailsford's disturbance.

At the cervicobrachial and the thoracolumbar areas where the curves reverse there may be an excessive kyphosis. There may also be a scoliosis particularly if the growth disturbance is greater on one side than on the other. In association with the deformity in the lower dorsal region the sternum pushes or actually buckles forward. The intervertebral disk spaces show considerably increased size in relation to both the wedged bones and the normal disk.

The ends of the long bones present involvement of the epiphyseal regions by mul-

irregular areas of ossification. There are widened joint spaces. Since growth interference may be asymmetrical this variation in growth plus weight bearing stresses will add to the deformity at a given joint. The epiphyseal centers in the tarsal and the carpal areas are delayed in making their appearance and when they do come in are abnormal in shape (Figs 99 to 108).

The later changes how the areas of involvement continuing to deteriorate with changes that might be foreseen becoming very severe. In the hips for instance deformity progresses and what had been well formed areas of ossification at the start first become malformed fragment then disappear and finally will show no epiphyseal re-ossification.

With the relaxation of muscle tone and the marked relaxation of ligaments there is a tendency for dislocations to occur particularly since the joints are not well formed. Not alone do the femoral necks and heads show abnormalities but so also do the acetabula. A hip will show marked disintegration and deformity from apparently two points of view (a) poor apposition of an abnormally shaped head against the acetabulum and (b) actual growth disturbance in the acetabulum itself (Figs 102 and 103).

Of course with these markedly abnormal joints such as in the hip and relaxation of muscles and ligaments dislocation easily occurs. In the knees fragmentation and growth disturbance cause severe deformity with severe knock knee as a rule (Figs 104 and 105). In the forearm the same sort of situation occurs in both the ulna and the radius with considerable bowing usually on the radial side with foreshortening of the ulna (Fig 108). There may be severe deformity of the ankle joint involving both the tibia and the fibula with fibular shortening (Fig. 107).

Pathology A biopsy specimen was reported upon by D. H. Shelling in Brenne mann's *Pediatrics*.⁸ He disclosed that the

biopsy of the shaft showed normal bone. Section of the epiphysis showed an irregular defective line of endochondral ossification with cartilage nests within the bony trabeculae. The metaphyseal trabeculae were porotic.



FIG. 108 Chondro osteodystrophy (Morquio-Brailsford) (From Dr M. M. Pomeranz) Upper extremity Child. Advanced changes involve the elbow and the wrist growth centers. Marked shortening, thickening and deformity of humerus, radius, ulna, metacarpals and phalanges are present.

No autopsy specimen has been reported upon to date

CHEMISTRY There have been no reported abnormalities in chemistry

Differential Diagnosis This must be differentiated from achondroplasia, gargoylism, spinal tuberculosis rickets hypothyroidism and osteochondritis, particularly of the Calvé type

THE ACHONDROPLASTICS These are strong dwarfs not feeble. They have if anything a severe lordosis. The trunk in an achondroplastic is basically normal. The limbs are relatively short. There are no gross epiphyseal or articular deformities (Figs. 73 to 76)

GARGOYLISM The features are grotesque. There is mental deficiency which is not present in Morquio's. The corneas are clouded. The spinal changes may be similar particularly with the slipper extensions anteriorly of the vertebral bodies but these do not usually occur in association with tongue projections from the centers of the bodies. This condition is also associated with defects in other body organs such as disturbance with the nervous system the endocrine system the urogenital system and the alimentary system. There is also enlargement of the liver and the spleen in gargoylism.

RICKETS. Although the kyphosis may be present, we do not have the tonguing or slipper formation. The extremities of the epiphyseal areas will show the typical cupping in a severe type. A history of vitamin-D deficiency can be obtained. If it be on the basis of deficiency as far as mineral absorption is concerned, this also will be evident. Where there has been vitamin D resistant rickets dwarfism and even deformity may be present. Radiograms will not show the Morquio pattern in the spine and the epiphyseal centers of the long bones. There will be metaphyseal cupping with osteomalacia of these areas of the epiphyseal centers in severe cases of the diaphysis also. No fragmentation is seen in the epiphyses (Figs. 186 to 200). Certain chemical changes may be evident, particularly a

tendency for elevation of the alkaline phosphatase.

HYPOTHYROIDISM There have been discussions of cases in which presumably bony changes occur. Certainly a delay in growth occurs and delay in the epiphyseal centers is distinctly so (Figs. 152 to 159). But here one may suspect it because of the facial characteristics the blood-cholesterol changes, as well as the studies that can be obtained by protein bound iodine and iodine uptake studies. Basal metabolic rates are important but are not as diagnostic as the above tests. Finally, of course, response to thyroid hormone is helpful.

CALVÉ'S DISEASE OF THE SPINE. There is an epiphyseal involvement in the young child in which there tends to be a platyspondyly. In this situation the primary ossification centers of the vertebral bodies appear to be affected more than the superior and the inferior epiphyseal plates. Therefore the wedging phenomenon would be less likely to occur; the platyspondyly would be more common and the deformity therefore would be simply that primarily of a flat vertebra.

TUBERCULOUS SPONDYLITIS. It is of course, important not to confuse these cases with tuberculosis of the spine. It is rare, however for tuberculosis of the spine to occur at the age of 3. Secondly, when it does occur the changes are primarily of the epiphyseal plates with secondary involvement of vertebral bodies. Third, there is evidence of constitutional disease. There is a tendency for fever, elevated sedimentation rate and positive tuberculin test.

VOORHOEVE'S DISEASE (OSTEOPATHIA STRIATA)

Definition. Osteopathia striata is a developmental abnormality characterized by striation of the skeleton, especially of the metaphyses of the long bones.¹

Incidence. The disease is rare.

Clinical Features: ROENTENOGRAPHIC APPEARANCE. The main features are long

itudinal striation in all the long bones (alternating with parallel lines of normal density in the metaphyses) and irregular fanlike striation of the ilium and a great increase in the density of the skull and the ribs.

Pathology There is linear or striated osteopetrosis. The lamellar structure is lost owing to obliteration of the canaliculi and the isolated lacunae appear small and evacuated.

Differential Diagnosis. The diagnosis of osteopathia striata is based entirely on the radiographic appearance. The physical examination and biochemical data are negative. The striation is characteristic and

appears in bones that are normal in other regards.

Treatment. Treatment consists in the surgical relief of any existent deformities where possible. Usually no treatment is needed.

Prognosis. The prognosis is usually good.

MYOSITIS OSSIFICANS PROGRESSIVA

(Syn. Fibrositis ossificans progressiva (Greig)¹ hyperplasia facialis ossificans progressiva² fibrocellulitis ossificans progressiva³)



FIG 109 Myositis ossificans progressiva in identical twins. (From Dr Jacob H. Vastine. These cases [Figs. 109 to 114] were published originally in *American Journal of Roentgenology and Radium Therapy* 59:204-212, 1948, and certain illustrations are reproduced with permission.) Identical twins C. M. and M. M., white females first seen at the age of 10 years in 1933 and followed until the present time (1955). Both cases began their difficulty with pain and stiffness in the cervical region. The backs of the twins show the paraspinal soft-tissue ossifications with a pressure area in M. M. who is not ambulatory.

Definition. *Myositis ossificans progressiva* is a rare congenital disorder which develops into progressive crippling due to aberrant but true bone formation throughout all muscle coverings of voluntary muscles. It is associated with such anomalies as short great toes and/or thumbs (Fig. 114). This true bone formation involves the muscle sheaths of practically all the voluntary muscles⁴ (Figs. 109 and 110).

Historical Notes. This condition is described originally by Guy Patin¹ and subsequently reported upon by Ferich,² who pointed out the short great toes of infants otherwise normal at birth. In 1868, von Dusch³ named the condition *myositis ossificans progressiva*.

The disease has been reviewed by Rosenstirn,⁵ Nutt,⁶ Mair,⁷ and Bank,⁸ the last in 1951.

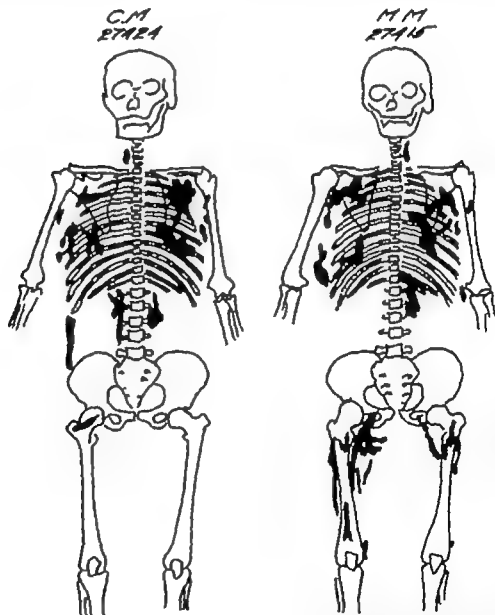


FIG. 110 *Myositis ossificans progressiva* in identical twins. (Same patients as Fig. 109.) Skeletal diagrams indicate the distribution of the soft tissue ossifications. The widespread changes about the hips of M M prevent her from walking. C M is ambulatory.



FIG 111 Myositis ossificans progressiva in identical twins. (Same patients as Fig 109) X ray pictures of the left hemithoraces and the shoulder girdles of the twins indicate the pattern of soft tissue ossification. The major bony bands are outlined for emphasis. Shoulder elevation is markedly restricted in both subjects

Etiology The cause of this extraordinary bone formation is unknown. However, the congenital microdactylia in 75 per cent of cases^{3,4} suggests a fundamental mesenchymal defect. It must be emphasized that this disease is different from the usual traumatic myositis ossificans.

Clinical Manifestations. There is little evidence that this disease is consistently hereditary or familial. There are isolated reported cases occurring in families and even in twins⁵ (Fig 109).

There is a sex predominance in favor of males.

At birth in at least 75 per cent of cases the stigmata of the disease (notably microdactylia and short abducted great toes and oftentimes thumbs) are present³ (Fig 114). Active evidence of the disease process may not make an appearance for some time. In rare instances, however, muscle changes have been observed also at birth.⁶

The general pattern for the appearance of this disease in active form is a latent period extending from the time of birth to as late as the thirty-fourth year. Sixteen per cent of cases show symptoms within the first year of life.³ Seventy-five per cent of cases occur before the sixth year of life.⁴

This extraordinary condition eventuates in rather complete bone formation throughout all voluntary muscle planes (Figs 109 and 110). It begins as an inflammatory reaction in the fascial planes. It usually starts in the posterior neck but may begin in any location. Trauma plays a role in some cases. It is not an etiologic agent but it can and does initiate the inflammatory reaction which eventuates in bone.

There is a distinct pattern in the development of this aberrant but true bone. It starts as a painful tender hot bluish and doughy mass. The muscle or muscles involved are swollen and indurated. The subcutaneous

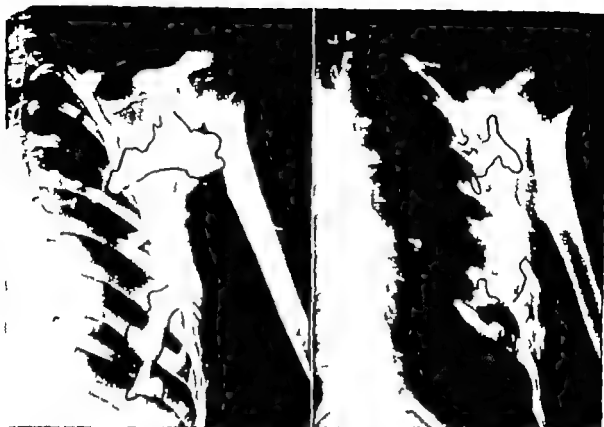


FIG. 112 Myositis ossificans progressiva in identical twins. (Same patients as Fig. 109.) Similar findings are noted in the roentgenograms of the right hemithoraces and the shoulder girdles. The prints are reversed.

tissue is edematous. The skin may be normal or reddened. This is often accompanied by systemic reaction such as fever up to 101° F.

After a few days the swelling decreases but the muscle remains indurated. This induration is relatively painless following the subsidence of the acute stage. Recurrent acute attacks simulating a rheumatic process involve ever widening areas.

Once a muscle's coverings have been involved by the initial inflammatory process, there is a varying interval during which quiescence, recurrent acute inflammatory attacks or progressive ossification are present. This interval may vary from weeks to months before it will be reactivated or progress to ossification. It is doubtful whether a muscular fascial plane, once involved, will escape eventual ossification.

Ossification will occur within weeks to months of the start of the inflammatory process, with the average time about 2 months. Eventually, this condition progresses to infiltration and bone formation in the coverings of almost all of the voluntary muscles of the body, including those of the jaw. The muscles of the eye, the facial expression, the act of swallowing, the tongue, the diaphragm, the heart, the perineum, the genitalia and the sphincters are said to remain uninvolved.⁴

A typical advanced case is a most unhappy but striking sight. One sees a slender individual with large ridges of bone scattered throughout the trunk and the extremities (Fig. 109). A frequent site of large bone masses is the back. The rhomboid muscles may be so involved that a veritable handle is formed transversely across the back. One



FIG 113 (Top) Myositis ossificans progressiva in identical twins. (Same patients as Fig 109) Left hips. Anteroposterior view. There is only a mild change in the hip of C, M whereas a complete ischiofemoral bony bridge is seen in the hip of M, M.

FIG 114 (Bottom) Myositis ossificans progressiva in identical twins. (Same patients as Fig. 109) Both feet. Anteroposterior views. Similar deformities are seen in the great toes of both the twins which present microdactyly, interphalangeal joint fusion, hallux valgus and abnormalities of the distal ends of the first metatarsals. Similar findings may be observed in the hands of patients affected with myositis ossificans progressiva.

can actually lift the unfortunate victim by these bone outgrowths.

The spine and the joints of the extremities may become fixed rigidly by bone bridges.

Teeth often must be removed to allow room for feeding.

The skin overlying the distal extremities and extending from the toes to above the ankles (like a sock for instance) varies in appearance and texture from the skin of the rest of the body. The involved zone of skin gives an appearance of decreased thickness and pigmentation loss like a vitiligo.

The great toes are abducted and shorter than the second toes. The interphalangeal joint may be ankylosed (Fig 114). The thumbs assume an appearance similar to that of the great toes.

The involvement of the muscles about the chest affects respiratory excursions so that

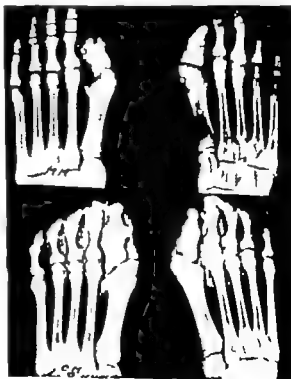




FIG 115 Myositis ossificans progressiva. (Same patient as Fig 109) C. M. 1954 now aged 30 years. Dorsal and lumbar spine Anteroposterior view. The extensive shoulder-girdle and the back soft tissue ossifications are shown clearly.

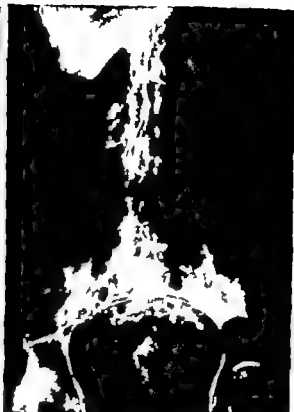


FIG 116 Myositis ossificans progressiva. (Same patient as Fig 109) C. M. 1954 now aged 30 years. Lumbar spine and pelvis. Anteroposterior view. Note the large staghorn formation arising from the left iliac crest. There is much new bone around the right hip area.

intercurrent infections of the lungs are common (Fig 115).

CHEMICAL FINDINGS All chemical studies are grossly normal including the alkaline phosphatase. Balance studies do not disclose a marked retention of phosphorus and calcium.¹⁴ Strangely the alkaline phosphatase repeatedly¹¹ performed in two cases when very intense bone formation was in progress was normal.

This finding is inexplicable on the basis of the present concept of the relationship of alkaline phosphatase to the ossification of bone. A possible explanation may be that this bone formation is by direct metaplasia. Alkaline phosphatase infers uncalcified osteoid.

RADI FINDINGS The normal skeletal components are unaffected except for osteoporosis and the congenital anomalies of the

hands and the feet. These anomalies are a reduced length of phalanges of the great toes and the thumbs. Occasionally the proximal phalanx may be so tiny as to be only a small wedge of bone. Sometimes the proximal phalanx is fused to the metacarpals or at the interphalangeal joint.¹⁵ Furthermore there is an abduction deformity of the great toe, a hallux valgus (Fig 114).

Throughout the trunk and the extremities will be observed large plaques of bone (Figs. 115 and 116). There may be large ridges or sheets of bone on the trunk or parallel with the shafts of the long bones. There may be bridges across the joints which represent ossification of ligaments

and tendons as well as of fascial planes (Figs. 111 to 113)

Finally, there are exostoses in relation to bony prominences such as the heels and the ischial tuberosities the supra-orbital ridges and the maxillae

Pathology The primary change is of the connective tissue in the intermuscular planes, and not of the muscle fibers themselves. The senior author has observed the uninvolved muscle to lie in an operative bed after careful dissection of the bone from the sheath.

The earliest changes are those of inflammatory swelling and connective-tissue infiltration of the intermuscular sheaths. Immature connective tissue and fibroblasts are seen microscopically to infiltrate the fascial planes between the muscle fibers and around the blood vessels.

The muscle fibers show a reactive swelling progressing to various types of atrophy and degeneration.

Finally, the connective tissue in the septa forms new bone by direct metaplasia with or without an intervening cartilaginous stage. This bone is indistinguishable grossly and microscopically from compact bone (Figs. 111 to 113, 115 and 116).

Treatment. There is to date, no known efficacious treatment. Excision of bone

bridges and plaques results in rapid recurrence. Avoidance of injury may retard the development of new sites of ossification.

Large doses of magnesium to nullify phosphorus with low calcium and phosphorus and vitamin D intakes were ineffective. Actually, balance studies were unchanged on this regimen in the presence of continued ossification. In other words, even though calcifying materials were restricted, ossification continued. No negative balance was evident, so calcifying material apparently was drawn from the skeleton.

Beryllium¹⁶ was also used with similar rationale in regard to phosphorus. It too was of no avail.

Prognosis. The condition is chronic and progressive. There are periods of remission. The eventual result is a widespread involvement and crippling resulting from immobilization of the joints of the extremity and of the torso. Finally, because of immobility and bone exostoses, the patients suffer from decubiti. They suffer lung infection because of the lack of respiratory excursion. They suffer from severe inanition because of their inability to ingest and masticate solid food.

Death occurs usually in late childhood or in early adult life. An occasional case may survive longer.

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Endocrine Disturbances

PRIMARY HYPERPARATHYROIDISM (PARATHYROID)

(Syn Parathyroidism fibrocystic disease; metaplastic malacia—von Recklinghausen hemorrhagic osteomyelitis—Barrie generalized osteitis fibrosa cystica)

Definition. Generalized osteitis fibrosa cystica is a metabolic disorder of adult life due to excessive secretion of parathyroid hormone that results in an elevated serum calcium a lowered serum phosphorus a negative phosphorus and calcium balance and progressive generalized osteoclasts of bone. It is associated frequently with giant celled tumors and cysts osteoclastic in nature (Figs. 117 to 133)

Historical Notes. The history of this interesting condition is associated with the history of the parathyroid glands for after all the bone change is a reflection of changes in the parathyroid gland

- 1700 The first recorded example of hyperparathyroidism appears to have been made by Courtial
- 1858 Remak described the parathyroid glands.
- 1864 Engel referred to cystic bone disease and disturbance of parathyroids
- 1876 Virchow reported the occurrence of cysts in long bones
- 1877 Langendorff referred to the concurrence of cystic bone disease and parathyroid disease
- 1879 Sandström¹ described the two superior parathyroid glands. He indicated that Remak in 1858 and Virchow in 1860 had described these glands
- 1884 Davies-Colley² reported the case of a young girl with generalized skeletal disease a tumor of the jaw renal

stones and increased renal excretion of calcium

- 1886 Rendfleisch reported cysts in long bones
- 1889 Hirschberg first described generalized variety of bone cysts in osteomalacia
- 1891 Von Recklinghausen gave the first accurate description of the condition and suggested the name osteitis fibrosa cystica.³ He discussed a bizarre disease of bone characterized by destruction and repair striking softening of the skeleton and the presence of cysts. He was unaware that any endocrine disorder might be associated with bony changes in question.³

It is of interest that Jung⁴ reinvestigated⁴ autopsy reports on two of the cases that von Recklinghausen had reported upon, one case in 1891³ and one in 1910.⁴ In both cases von Recklinghausen had found what was apparently a parathyroid adenoma, but had mistaken it for a lymph gland. It must be considered that, in 1891³ von Recklinghausen differentiated this case Jung refers to from osteitis deformans, osteomalacia and osteolytic cancer. In the 1910 monograph⁴ von Recklinghausen differentiated this case from rickets and osteomalacia. Albright clearly points out that case 5 and probably case 6 described by von Recklinghausen in 1891 as osteitis fibrosa generalisata, in reality was polyostotic fibrous dysplasia.

- 1891 Gley rediscovered the superior parathyroid glands.
- 1896 Kohn⁵ for the first time described the inferior parathyroids
- 1896 Vassale and Generali⁷ were among the first to recognize the function of the

parathyroids. They showed that tetany was the result of excision of the parathyroid glands.

- 1897 Welsh⁸ described the morphologic features in the normal parathyroid glands. He called attention specifically to the oxyphil cell in contradistinction to the chief cell. He believed that the least specialized cell was the water clear one (wasserhelle) which was transformed in time into the chief cell.
- 1904 Askanazy⁹ first suggested that there might be an association between von Recklinghausen's disease and hyperparathyroidism. He gave a clinical description of a patient with generalized bone disease, multiple fractures and a tumor of the parathyroid gland.
- 1905 MacCallum¹⁰ reported a case of chronic glomerulonephritis as a manifestation of activity of a parathyroid adenoma. It is of interest however that the probable explanation was hyperparathyroidism secondary to the nephritis.
- 1906 Erdheim¹¹ believed that parathyroid enlargement was secondary. He was probably the first to recognize more than a causal relationship between the body changes and the hyperplasia of the parathyroid glands in cases of osteomalacia. His observation was correct; his conclusion of gland hyperplasia secondary to bone changes was in error according to modern concepts.
- 1909 MacCallum and Voegtlin¹² showed that parathyroidectomy led to a fall in serum calcium, although later studies indicated that the primary action was a rise in serum phosphorus owing to its decreased urinary excretion.
- 1915 Schlagenhauser¹³ suggested the removal of the diseased parathyroid as a cure for malacic osseous disorders but because of Erdheim's hypothesis they were afraid to attempt this. Even Mandl transplanted parathyroids and found the condition worsened before he removed the gland for this disease.
- 1925 Mandl¹⁴ extirpated a parathyroid tumor in a case of hyperparathyroidism with dramatic relief of pain in 1 month and regression of condition.
- 1926 The work of Collip¹⁵ clearly delineated proof of the relationship between parathyroid activity and the metabolism of phosphorus and calcium. His discovery of the parathyroid hormone led at once to study of its effects in normal persons. This hormone is still used clinically and experimentally. It must be given parenterally. Soon examples of bone disease associated with hyperfunction of a parathyroid tumor became known—as in the generalized osteitis fibrosa of von Recklinghausen.
- 1930 Barr and Bulger¹⁶ stressed the metabolic and the skeletal changes in hyperparathyroidism.
- 1930 Jaffe, Bodansky, and Blair¹⁷ injected parathyroid hormone in animals and produced the characteristic bone lesions of fibrocystic disease.
- 1931 Camp and Ochsner¹⁸ first described subperiosteal reabsorption of bone in primary hyperparathyroidism.
- 1937 Albright¹⁹ *et al* wrote of renal calculi in association with parathyroid adenomas or hyperplasia with or without decalcification of the skeletal structures. They called attention to the fact that renal calculi are sometimes the first clinical manifestation of the disease.

Incidence. Primary hyperparathyroidism is fairly uncommon. In the last 10 years, for example, among 109,000 admissions at Lambeth Hospital (London) there have been only 2 afflicted persons. It is possible, however, that the disease is not diagnosed correctly as frequently as it might be particularly in its early phases.

Osteitis fibrosa cystica is twice as common in women as in men. It occurs at all ages but usually in middle life. In children the incidence is equal.



FIG 117 Primary hyperparathyroidism. (From Dr M M Pomeranz) Pelvis. Anteroposterior view. Cystic areas in the iliac bones and the right femur represent osteoclastomas filled with fibrous tissue. The generalized osteoclasts is very mild in this instance.

FIG 118 Primary hyperparathyroidism (From Dr M M Pomeranz) Elbow and forearm. Anteroposterior view. The dramatic finding is the cystlike osteoclastoma in the distal humerus. The more important diagnostic feature is the osteitis fibrosa of the forearm bones as evidenced by medullary widening, coarsened trabeculations and cortical thinning. The demarcation between the cortex and the medullary cavity is less distinct. Blood chemical and urinary studies help distinguish primary hyperparathyroidism from renal osteitis fibrosa.



Etiology The etiology of this condition has been indicated in the historical notes. There appears to be no doubt that primary osteitis fibrosa generalisata is due to hypersecretion of the parathyroid gland or glands. This can be due to hyperplasia of the parathyroid or to a secreting adenoma.

The adenoma is more apt to be located in the inferior glands, 84 per cent to 16 per cent in the superior glands.²⁰

This disease is characterized by changes in the parathyroid glands, in bone and in soft tissues, particularly the kidneys. Primary hyperparathyroidism has been related to a primary adenoma, a primary carcinoma of a single gland, an adenoma of more than one gland or hyperplasia of all the glands. Although cases of hyperparathyroidism associated with hyperplasia of all the glands

have been reported, it is the authors' opinion that primary hyperparathyroidism or osteitis fibrosa generalisata will result only from an adenoma or a carcinoma of a single gland. If hyperplasia of all of the glands occurs, it would be more reasonable to presume that this represents a case of secondary hyperparathyroidism from one of the many causes that can produce secondary hyperparathyroidism, which is discussed under that heading.

It appears that the important cell in the parathyroid adenoma of secreting type is the chief or principal cell. Two other cells are observed—a water-clear or *wasserhelle* cell and the oxyphilic cell. It appears that the active cell is the chief cell. The chief cell represents the secretory phase of the cellular cycle of the gland; the water cell is



FIG. 119 Primary hyperthyroidism. (Case originally studied on the service of Dr. A. Bruce Gill by the senior author. From *J. Bone & Joint Surg.* 18: 942-947, 1936.) White female 31 years old. Lower femora and tibiae. Anteroposterior view. Generalized osteoclasts with localized expansile osteoclastomas. These so-called "brown tumors" of von Recklinghausen simulate cysts roentgenographically.



FIG. 120 Primary hyperparathyroidism. (Same patient as Fig. 119.) (Gill, A. B., and Stein, L. *J. Bone & Joint Surg.* 18: 943, 1936.) Tibiae. Lateral view. Sixteen months following removal of two normal parathyroid glands and the utilization of a consistently high-calcium high-phosphorus and high vitamin D intake. The average daily intake was phosphorus 3.0 Gm., calcium 2.0 Gm., vitamin D 10,000 units. Average daily retention was phosphorus 1.5 Gm., calcium 1.0 Gm. Marked healing of osteoclastic bone and osteoclastomas is evident. The cystlike spaces are now dense and solid. One true cyst in the tibial mid shaft has not healed.

simply a transitory stage in the development of a chief cell. The oxyphil cell on the other hand appears to be a resting cell without any clear-cut action so far as has been demonstrated.

Clinical Features. Albright and Reifenstein²² list the clinical findings under three headings: (a) involvement of the skeleton, (b) urinary tract changes and (c) changes secondary to hypercalcemia. It has been considered that true primary hyperparathyroidism must demonstrate all of these factors. Analysis of cases, however, indicates that hyperparathyroidism may present only one of these findings. On the other hand, it may combine two or all three.

It is of particular interest to point out that skeletal manifestations are less frequent than renal ones, this despite the original classification of this disease as skeletal.

1 INVOLVEMENT OF SKELETON. The skeletal changes are: (a) decalcification which ranges from minimal absorption of bone to practically complete erasure of the skeleton—in this latter phase the shadow cast by the bones upon x-ray film may be hardly denser than the surrounding soft tissues. (Contrast Figures 117, 118, 132 and 133.



FIG 121 Primary hyperparathyroidism (Same patient as Fig 119) (Gill A B., and Stein I J Bone & Joint Surg. 18 945 1936) Left femur Anteroposterior view Giant-cell osteoclastoma occupying most of the left femur In addition, expansion of the upper femoral shaft is noted The bone appears hazy and is so porotic that its shadow is barely denser than the surrounding soft tissue (The print is reversed)



FIG 122 Primary hyperparathyroidism. (Same patient as Fig. 119) Left femur Anteroposterior view Giant-cell osteoclastoma of the left femur 16 months later following the regimen outlined in Figure 120 Note the dense trabeculations throughout the healed osteoclastoma Bone is now so dense that x ray exposure great enough to obliterate soft tissue shadows still shows bone in sharp contrast. Contrast with Figure 121 and later with Figure 131

with the advanced changes of Figures 119 to 131) (b) Deformities of bone due to excessive decalcification of the skeleton which therefore bends and twists. Further deformities may result from pathologic fracture.

Finally true cysts and osteoclastomas (pseudocysts) may be found The osteoclastoma often is manifested as a giant-cell epulis in the jaw Therefore the dentist oftentimes may discover a case of hyperparathyroidism

The deformities may vary as does the degree of bone absorption A patient may show little or no deformity or may become so deformed that he lies helplessly a mass of twisted nodular limbs with a collapsed

sternum and rib cage and shortened curved spine

Early cases may present only bone pain. Late or advanced cases have pain too but show changes from minimal to complete obvious involvement.

It has been observed numerous times that ingestion of large quantities of milk may prevent absorption of the skeleton²⁴ The reason of course is that a quart or more daily of milk replaces the calcium and the phosphorus lost from the skeleton. It must be remembered that, in hyperparathyroidism, excess calcium and phosphorus excretion through the kidneys must occur Simple replacement of the calcium and the phosphorus will merely balance calcium and phosphorus loss It will not reduce the



FIG 123 Primary hyperparathyroidism. (Same patient as Fig. 119) (Gill A. B., and Stein, I. J. Bone & Joint Surg. 18 945 1936) Right femur Anteroposterior view on admission is on the right of the illustration and shows extensive osteoclasia with a large defect in the lateral portion of the mid-shaft. Sixteen months later healing reaction is observed in the left hand roentgenogram. For treatment, see the caption of Figure 120



FIG 124 Primary hyperparathyroidism. (Same patient as Fig. 119) Chest and dorsolumbar spine on admission. Despite very low x ray exposure, very little bone detail can be observed. The rib cage has become deformed and collapsed. Cysts can be seen in a few ribs.

"load" upon the kidneys nor the danger of predisposing to kidney involvement and disease (Figs 122 123)

2 **RENAL INVOLVEMENT** This is secondary to the enormous excretion of calcium and phosphorus in the urine. At least 50 per cent of hyperparathyroid cases present some form of urinary tract pathologic changes.

In a nation such as the United States where good nutrition and widespread use of dairy products prevail kidney involvement will often precede bone change. There are primarily two types of kidney involvement.

1 That due to deposition of calcium and phosphorus stones in the kidney, the renal pelvis or the ureters. These stones may range from tiny ones to large staghorn

calculi filling and obstructing the renal pelvis.

2 That due to deposition of calcium and phosphorus in metastatic forms in the kidney parenchyma with special emphasis upon the kidney tubules. This is called nephrocalcinosis. The interstitial tissue may be involved also by metastatic calcification.

In the normal acid urine the stones will be calcium phosphate or calcium oxalate. If infection transpires the pH of the urine may rise. Then the stone may have additional coatings of other electrolytes relatively insoluble in an alkaline medium—magnesium and ammonium in combination with phosphate. Staghorn calculi are usually phosphate or cystine stones.

Mechanical blocking of urine output may lead to considerable kidney destruction and infection.



FIG 125 Primary hyperparathyroidism (Same patient as Fig. 119) Pelvis and lumbar spine on admission Anteroposterior view A severe degree of osteoclastic change and deformity is present.



FIG 126 Primary hyperparathyroidism. (Same patient as Fig. 119) Left forearm on admission Anteroposterior view Characteristic osteoclastic reaction in all bones and osteoclastoma formation with expansion in ulna. There is a small cyst in the radius and a loss of definition between the medullary cavity and the cortex in the radius and the ulna.

Nephrocalcinosis may produce severe kidney destruction. Early it may be manifested by polyuria and polydipsia with a secretion of a urine of fixed specific gravity. Later signs of azotemia (nitrogen retention) with phosphate retention occur. At this stage blood chemistry may be confusing for now an increased blood phosphorus rather than a decreased one would be found. However the blood calcium may also show elevated levels here but tend to approach normal or subnormal values as phosphorus rises.

Symptoms and blood and urine findings will be related to the type and the degree of kidney involvement.

For instance when nephrolithiasis or ureterolithiasis is the predominant factor acute renal colic infection and hematuria are cardinal findings which bring this patient the attention of the urologist. Intensive work up of such patients has resulted in the frequent diagnosis of hyperparathyroidism. Attention then must be directed to the endocrine cause.

In nephrocalcinosis the kidney disease

may also present findings associated with tubular disease. These may be summed up as follows: loss of base economy, failure to reabsorb amino acids and selective failure of calcium reabsorption.

3. HYPERCALCEMIA Symptoms of hypercalcemia found in hyperparathyroidism may be listed as follows: hypotonia and decreased excitability of muscles. This refers to skeletal, smooth and cardiac muscles. It has been suggested that it is this lack of tone which gives rise to constipation, anorexia or poor appetite and lassitude. Intermittent nausea with progressive loss of weight, and vomiting which is often intractable also are ascribed to hypercalcemia. Patients frequently complain of abdominal

pains and cramps so that there are clear-cut signs and symptoms suggesting gastric ulcer or appendicitis. Numerous cases have actually undergone surgery for ulcer due to these symptoms.

Calcium deposits may occur in the deep conjunctiva of the palpebral fissure and there is also a band keratitis.²²

CHEMISTRY The primary factor in the hyperparathyroid state is the increase in phosphorus outpouring through the kidney with resultant lower blood phosphorus. This then becomes associated with increase in calcium excretion through the kidney with resultant elevation of blood calcium.

The alkaline phosphatase is usually elevated since bone-productive efforts are constantly going on and cannot be completed in view of the fact that the decalcification is a predominant picture.

When renal complications occur certain additional and sometimes confusing blood chemical changes may be observed as indicated in the preceding section on kidney involvement in this disease.

Balance study indicating the amount of measured intake of calcium and phosphorus and the measured output shows a loss of calcium and phosphorus from the body with an increased output through the feces but markedly increased and even reversed output of calcium and phosphorus through the urine. Normally, approximately 80 per cent of calcium and phosphorus excretion through the body is fecal. In hyperparathyroidism, this may be reversed.

A summary of the chemical findings in hyperparathyroidism reveals a lowered blood phosphorus, an elevated blood calcium, an elevated alkaline phosphatase and an increased output of calcium and phosphorus from feces and urine with reversal of urine-fecal output ratio.

Normally, fecal calcium is 3 to 5 times that of urinary calcium on a low calcium diet. (See page 30.) Absolute values in the normal individual per day are 100 to 150 mg of calcium in the urine, 300 to 400 mg in the feces.

In hyperparathyroidism on a low calcium diet urinary calcium rises above the critical level of 150 mg per 24 hours and may reach levels as high as 500 to 600 mg per day. Fecal calcium is also elevated but lags behind the urinary excretion unless secondary renal changes interfere with calcium excretion.

ROENTGENOGRAPHIC FINDINGS We may consider x ray features as a shadowgram of the gross pathology of the bone lesion. Roentgen examination nevertheless does have limitations. These can be overcome to some degree by understanding the underlying gross pathology.

Radiographic findings in hyperparathyroidism vary from no appreciable change in bone structure to practically complete dissolution of the skeleton in a widespread fashion.

When the intake of calcium has been inadequate to maintain balance and the condition has been progressive long enough considerable bone absorption occurs. In this instance we would find generalized increased radiolucency of the skeleton. In this condition the loss of bone substance is primarily that of a generalized decalcification which may be associated with some increased fibrosis of the bone structure. At this stage the trabeculae are present but they become thinned with associated widening of the haversian canals (Figs. 117, 118, 132 and 133). This is in distinct contrast with true osteoporosis in which there is a failure of bone matrix production. Osteoclasts are actual reabsorption of bone matrix. In this condition trabeculae are absorbed not merely thinned. End stages of both conditions can be confused radiographically. However other variations in bone involvement as well as the clinical pictures and the chemistries will aid in differentiation.

We may consider that the osteoclastic process of hyperparathyroidism is primarily one of decalcification and that it may vary in degree. As the osteoclasts of the skeleton progresses the roentgen shadow becomes more and more radiolucent. Eventually the



FIG. 127 Primary hyperparathyroidism. White female (same patient as Fig 119 now 41 years old). Right femur 10 years after removal of two normal parathyroids and institution of high-calcium, high phosphorus and high vitamin D diet which was maintained for 3 years. See Figure 123. It is quite probable that the secreting adenoma continued to function and may well have been in the mediastinum. At any rate the patient presented signs of kidney damage 10 years after parathyroid excision. At this time the osteoclastic reaction appears to have recurred. Although some dense trabecular detail appears in lines of stress, the over all pattern of bone is poor. Her chemical studies at this time showed calcium 12 mg. per 100 cc. phosphorus 3.0 mg. alkaline phosphatase of 18 Bodansky units. These may be compared with findings of calcium 14.0 mg. per 100 cc. phosphorus 3.2 mg. phosphatase of 20 Bodansky units before parathyroidectomy. A less intense reactivated hyperparathyroid state appears to be present.

bone may show little contrast with the surrounding soft tissues (Fig 121). This bone absorption and fibrous tissue replacement may progress to a final stage in which it is difficult to determine the shadow of the bone structure in relation to the surrounding shadow of soft tissues (Figs 124 and 125). This may be the only radiographic finding in parathyroidism.

In addition to the picture of generalized bone decalcification three additional skeletal lesions are often observed:

1. Small cysts usually subcortical which are lined with a fibrous membrane (Fig



FIG. 128 Primary hyperparathyroidism (Same patient as Fig. 119 now 41 years old. See Fig 127). Ten years after parathyroidectomy. Both tibiae. Contrast recurrent progressive osteoclasia with Figure 120 which shows the leg bones while the patient was on a calcifying diet.



FIG 129 Primary hyperparathyroidism (Same patient as Fig. 119 now 41 years old. See Fig. 127) Dorsolumbar spine. Lateral view Severe generalized osteoclasts with dense trabeculae at stress points. Note longitudinal striations resembling osteolytic Paget's disease.



FIG. 130 Primary hyperparathyroidism. (Same patient as Fig. 119 now 41 years old. See Fig. 127) Skull. Anteroposterior view Diffuse changes of osteoclastic type associated with over-all enlargement of the calvaria. This is a severe degree of osteitis fibrosa generalisata following longstanding excess parathyroid hormone action on the skeleton

126) These will not fill in in the healing stage of the disease (Fig. 123)

2 Scattered small (and often large) cysts which are expansile in nature They may be so big as to often appear to distend the entire cortex in a uniform circumferential way The appearance is much like a balloon which is blown up and expands evenly in all directions These lesions are not cysts they are not empty spaces in bone as they appear to be on x ray films. They are osteoclastomas and are filled largely with giant-cell (osteoclast) stroma. These structures also contain some osteoblasts and reticulum cells. In the healing stage these "cysts" rapidly

condense and recalcify (Figs 119 to 122 128 and 131)

3 Moderate variations of these osteoclastomas are the "giant-cell brown tumors of von Recklinghausen" which also are osteoclastomas but contain moderate amounts of abortively calcified bone

These osteoclastomas of both type 2 and type 3 frequently are observed in the calvarium, the maxilla the mandible and the zygoma (Fig 130) Therefore frequently the dentist may identify this disease either by the appearance of these osteoclastomas on dental roentgenograms or by identification of giant-cell epulis either roentgenographically or clinically In addition a dental finding nearly pathognomonic of this disease is the absence of the lamina dura.

The general appearance of the skull aside from the osteoclastomas is that of a ground



FIG 131 Primary hyperparathyroidism. (Same patient as Fig 119 now 41 years old. Recurrence after parathyroidectomy. See Fig 126.) Left femur Anteroposterior view. Progressive osteoclasts and bowing with dense trabeculations in response to stress lines. Compare with Figures 121 and 122. The large osteoclastoma is undergoing active destructive changes again.

glass texture (Fig 132). This is due to progressive decalcification with generalized thinning of trabeculae and infiltration of fibrous tissue.

The osteoclasts involving the entire skeleton results in frequent bending and twisting of long soft bones. These may be the site of multiple minute compressions and fractures which form deformity. They may also develop complete pathologic fractures. Such fractures often deform because they heal by malunion.

The vertebrae are so softened that the



FIG 132 Primary hyperparathyroidism. (From Dr M. M. Pomerans) Skull. Lateral view. In contrast with Figure 130 only changes of osteoclasts are seen. These changes are often called osteoporotic. Actually, the roentgenogram cannot distinguish between osteoclasts, osteoporosis and osteomalacia. This is a typical ground-glass appearance with trabecular coarsening and loss of contrast between the diploë and the tables.

tense nucleus pulposus compresses contiguous vertebral bodies in a biconcave or cod fish vertebra fashion (Fig 129).

Summary of Roentgen Features

- 1 Osteoclasts and generalized progressive decalcification. This bone erosion shows as a worm-eaten appearance. The generalized decalcification is manifested further by a relative widening of the medulla and cancellous areas with a relative thinning of the cortex. There is diminished contrast between cortex and cancellous and medullary zones as well as between bone and surrounding soft tissue.

- 2 Small usually subcortical cysts.

- 3 Osteoclastomas either empty appearing spaces or trabeculated expansile tumor

- 4 Giant-cell epulis
- 5 Absence of lamina dura.
- 6 Frequent deformities associated with bending and twisting of bones and with pathologic fracture and nonunion
- 7 Biconcave (codfish vertebrae) compression of vertebral bodies due to pressure of disk upon softened contiguous bone

Pathology The primary lesion is the parathyroid tumor which has been described fully under etiology. The entire skeleton is involved but may show variations from minimal changes to nearly complete bone absorption.

The following salient gross and microscopic findings are characteristic of this bone disease.

1 Generalized skeletal osteoclasts results in bone that is softened and may cut easily. The cortex and cancellous and medullary zones become less distinct. Deformities such as bending, twisting, fractures, malunions, vertebral compressions and sternal and rib collapse occur (Figs. 119 to 131). These findings may not be observed grossly in mild or early cases (Figs. 117, 118, 132 and 133). However, the microscopic findings will be evident in all stages.

Microscopically the primary osteoclasts begins in the Howship's lacunae. The exact mechanism of bone reabsorption is still not solved fully. As described in Part One, it has been observed that contact of parathyroid gland to bone alone will cause bone absorption without osteoclast proliferation. This, however, cannot be the only mode of action.

Marked proliferation of osteoclasts and osteoclastic activity is a definite part of the microscopic findings in clinical hyperparathyroidism. The trabeculae are dissolved through expanding absorption radiating from the lacunae. Progressive decalcification followed by marrow fibrosis results in a worm-eaten appearance of the bone. The haversian canals become involved with marked and progressive dilatation of their lumina. This continues until cortical bone becomes cancellous bone and until only a thin cortical shell remains. The pattern of



FIG. 133 Primary hyperparathyroidism (From Dr. M. M. Pomeranz). Right hand and wrist. Anteroposterior view. Roentgenograms of the hand are not often studied in this entity. Note the so-called cysts whose etiology is confirmed by the trabecular coarsening and the loss of density in all the bones. The osteoclasts of hyperparathyroidism is always generalized.

haversian canals in cortical bone becomes irregular and disorganized. Thereby this pattern stimulates porotic cancellous bone.

2 Marrow fibrosis. Coincident with generalized osteoclasts is the usually overlooked process of marrow fibrosis. It is overlooked as a rule because the clinician cannot observe it in the roentgenogram and biopsies are not obtained as frequently or as easily as radiographs.

The findings in marrow fibrosis may be listed as (a) increased marrow vascularity, (b) proliferation of granulation tissue to fill the fatty marrow spaces with fibrous tissue, (c) this proliferating granulation

tissue not only invades the medullary cavity and the intertrabecular spaces but also disseminates throughout the cortex (d) the granulation tissue gives rise to abortive bone formation of fiber or woven type. This is in contrast with normal lamellar bone.

3 Osteoclastomas which occur frequently in this disease as it progresses. This is the typical brown tumor of von Recklinghausen and must be differentiated from true giant cell tumors (Figs 119 to 123, 126 to 128 and 131).

This lesion of hyperparathyroidism is brown in color, shows gross hemorrhage and is gelatinous in structure. It may contain bone trabeculae in varying amounts or none at all. When present these trabeculae have a gritty consistency. When bone trabeculae are present these will show in the x-ray picture. Both the trabeculated and the non-trabeculated lesions are the same. However, x-ray picture discloses that the trabeculated ones have been considered erroneously to be giant-cell tumors in contrast with the non-trabeculated which often have been considered to be cysts. It is well to bear the pathology of these lesions in mind and not to make an interpretation upon x-ray findings alone.

Microscopically these osteoclastomas are composed of masses of osteoclasts. These may frequently coalesce to form giant cells. These tumors should not be confused with giant-cell tumor. The best differentiation between the two is that in the parathyroid lesion the predominant structure is giant cells which are collections of osteoclasts with associated hemorrhage and necrosis. Whatever stroma is present here is of mature fibroblast type with bone trabeculae.

In giant-cell tumor paradoxically the pathognomonic cell is not the giant cell but the stromal cell. This is a large mononuclear cell with cytoplasmic processes whose origin is not necessarily established. Geschickter²¹ holds the origin in an abnormal manifestation of osteoclasts. Lichtenstein²² considered their origin to be from nonosteogenic supportive tissue of the marrow. In any event

it is the stroma here, not the giant cell which is important.

The osteoclastoma heals when the parathyroid tumor is removed as opposed to the cystic lesion which is next described, from which it is often indistinguishable in the roentgenogram.

4 Cysts. These may be unilocular or multilocular. They may or may not contain fluid or fibrin and usually are found subperiosteally in the cortex (Fig. 126). The walls of these cysts contain a fibrous lining of nearly avascular fibrous tissue. Considerable collections of osteoclasts may surround these cysts. The origin of these cysts is unknown. They remain unchanged when healing in this disease occurs.

Since we know that parathyroid hormone in itself can produce a considerable amount of bone absorption by direct action, it is possible that these cysts represent direct effect of concentrations of parathyroid hormone. We know also that parathyroid hormone tends to stimulate osteoclasts and possibly osteoclast formation and for that reason we may expect numerous cells of this type in the walls and since all bone-structure detail has been erased in these cysts, when healing occurs in this disease they will not fill in in contrast with the osteoclastomas which do.

5 Abortive healing is observed as nature's effort to form new bone. It is observed in denser staining trabeculae with formation of fiber osteoid bone. This type of fiber osteoid represents an attempted healing, particularly in stress areas. This occurs because stress adds another stimulus to bone formation. Areas in which this type of bone trabeculae occurs include the concave side of bending deformities and areas of fracture.

Differential Diagnosis. This condition must be differentiated from osteomalacia. Very important in this differentiation is the fact that the decalcification of bone is present here too but cysts and osteoclastomas are not found (See Table 8, p. 468).

Rickets, of course, must be differentiated from juvenile forms of hyperparathyroid

TABLE 5

	ETIOLOGY	CLINICAL
Hyperparathyroidism, primary	Hyperplasia or hypersecretion of parathyroids	Nephrolithiasis Nephrocalcinosis Skeletal absorption and deformity Hypercalcemic symptoms
Hyperparathyroidism, secondary	Kidney disease producing secondary hyperparathyroidism	Adults — indistinguishable from above Children — superimposed renal rickets and dwarfism
Osteitis deformans	Unknown	Bone deformity Skull enlargement Osteolytic change in bone followed by osteoblastic reaction Kidney stones
Osteomalacia	Defect in vitamin D supply and/or calcium and phosphorus intake in adults	Skeletal decalcification, fracture and tendency to deformity
Rickets	Defect of vitamin D and/or calcium and phosphorus in children	Disturbance of normal bone growth, skeletal decalcification and deformity. Also if uncontrolled, dwarfism
Fibrous dysplasia	Mesenchymal defect	Café au lait spots. Tendency to unilateral involvement. Deformity especially of hip Pathologic fracture
Osteoporosis, postmenopausal and senile	Lack of gonadal and adrenal secretions — loss of protein matrix	Bone absorption — chiefly of matrix. Observed in older people especially women. Pain in back, often girdle radiation vertebral changes
Multiple myeloma	Plasma-cell neoplasm	Generalized pain. Weight loss, malaise anemia Pathologic fractures, no pre-existing deformity May occasionally have some hypercalcemic symptoms but not usually
Carcinomatosis	Neoplasm metastasizing to bone	Rapid deterioration of patient Weight loss History of primary focus Possible hypercalcemic symptoms

TABLE 5 (Continued)

CHEMICAL	ROENTGENOGRAPHIC
Low serum phosphorus, high serum calcium Marked hypercalcuria and hyperphosphaturia Elevated alkaline phosphatase Balance studies show negative balance of calcium and phosphorus with greater loss through urine	Skeletal decalcification Scattered small cysts Osteoclastomas, with and without calcified trabeculae Ground-glass appearance of skull Pathologic fractures, deformities Soft-tissue calcifications
High serum phosphorus. Normal or moderately lowered serum calcium. Azotemia Balance studies show negative balance of calcium and phosphorus with greater loss through stool Elevated alkaline phosphatase Albuminuria, acidosis, low CO_2 . Low serum sodium. High serum chloride	Same as above
Elevated alkaline phosphatase Tendency especially on fixation or bed rest, for elevated serum calcium with hypercalcuria Balance studies show retention of calcium and phosphorus. Loss of sulfur and magnesium	Osteolytic advancing wedge followed by osteoblastic reaction. Dense trabeculae. Diffuse involvement Enlargement of involved bones Numerous microfractures causing pain and deformity. Pathologic fractures of transverse type
Normal or lowered serum calcium Phosphorus decreased Elevated serum alkaline phosphatase, negative calcium and phosphorus balance	Skeletal decalcification, pathologic fracture, no cysts or tumors. Looser lines—(symmetrical pseudofractures)
Same as above	Knobbing at the epiphyseal ends of bones with increased width and length of the epiphyseal plate zones. Metaphyseal cupping Decreased density of the epiphyseal centers occurs and eventually generalized decalcification of bone may be seen
No abnormal chemistry	Usually unilateral involvement Some broadening of involved bone with cysts. No expansion of cortex by large cysts Shepherd's crook deformity of hip
Lowered urinary estrogens. Other studies negative, except negative calcium and phosphorus balance Semle form may show lowered urinary 17 ketosteroids, due to decreased adrenal androgen function	Marked absorption of bone structure changes most marked in spine, "codfish vertebrae." Biconcave compressions in lumbar region usually with flattening of the lumbar area and wedge compression in the dorsal. Marked thinning of compact layer of bones. Poor bone trabeculae
Blood cellular changes. Elevated calcium Reversal A/G ratio. High plasma protein. Bence Jones proteinuria	Picture varies from no change in bone to multiple punched-out areas involving all bones. No reaction about margins of lesions Pathologic fracture not uncommon
Elevated alkaline phosphatase in osteoblastic type May have elevated serum calcium in osteolytic type In carcinoma of prostate alkaline and acid phosphatase are elevated	Pathologic fracture common Marked irregular destruction of bone in osteolytic type—no reaction about edges. In instance of carcinoma of prostate and other osteoblastic lesions, shows marked increased bone density

ism Both present a picture of decalcification and lack of bone formation The latter is due to inadequate calcification of the provisional zone of the epiphyseal plates

In addition to differentiation on a basis of osteoclastomas in parathyroidism and not in rickets or osteomalacia distinct differentiation can be made by chemical studies

Other conditions that must be separated from hyperparathyroidism are: metastatic carcinoma, multiple myeloma, giant-cell tumor, unicameral bone cyst, polyostotic fibrous dysplasia, Paget's disease and osteoporosis—either postmenopausal or senile.

The clinical picture of all these conditions will help in differentiation, the chemical characteristics and the pathologic picture will complete the delineation. (See Table 8, p. 468.)

Treatment. It may be noted from what has been stated above that even severe hyperparathyroid states of primary type could be controlled by an adequate intake of calcium, phosphorus and vitamin D. This, however, would require enormous intakes of calcium and phosphorus with tremendous excretion of calcium and phosphorus through the urine. The danger of such a situation is quite great in regard to the possibility of nephrolithiasis, nephrocalcinosis and calcification of metastatic type involving the kidney parenchyma and other soft tissues.

The best approach from the over all point of view with the greatest amount of safety for the future of the patient, is in the identification and the removal of the parathyroid adenoma. It must be borne in mind that a specific physiologic pattern is present in a patient who suffers from primary hyperparathyroidism, particularly if it is to a severe degree. The primary effect of excess parathyroid secretion is upon the kidneys and bone. The findings included in this pattern are: (a) hypercalcemia, (b) hypophosphatemia, (c) negative calcium and phosphorus balance, (d) severe osteoclasia and (e) high alkaline phosphatase indicating large amounts of uncalcified osteoid tissue which is hungry for calcification.

To corroborate this, we may observe even in active hyperparathyroidism an abortive process of calcification concurrent with the severe primary osteoclasia which is a part of this condition.

Treatment requires removal of the parathyroid adenoma plus care to sidestep complications. Complications are less likely where no bone involvement has occurred. Therefore emphasis herein is laid primarily on treatment of the more severe form—hyperparathyroidism with bone involvement.

The moment the responsible secreting adenoma is removed, marked chemical and physiologic sequelae will at once come into effect. The kidney function will tend to return to the normal type so that the blood phosphorus will rise, the calcium fall. The skeleton, previously a site of osteoclasia, at once begins to heal and consumes every bit of calcium and phosphorus available. This produces a severe drop in blood-calcium levels. Severe tetany will quickly ensue unless steps to avoid this complication are taken promptly. Actually the need is to anticipate complications, not to wait for them to develop in full blown form, for then complications are much harder to handle.

The major problem is the excess affinity of the hungry bones for calcium in particular. The alkaline phosphatase level will remain elevated as long as there is any appreciable amount of uncalcified matrix.

With cessation of osteoclasia, the hungry bones rapidly absorb all available calcium and phosphorus to develop calcified osteoid. This marks the start of a healing process in bone which is contrasted with the previous osteoclasia. The immediate effect, therefore, is a further lowering of the blood phosphorus and a precipitous drop of the elevated blood calcium. This drop goes to subnormal levels. The kidneys respond and resume their previously normal type of function—they again reabsorb glomerular filtrate phosphorus through their tubules.

Despite this now normal kidney mechanism, the bones are so hungry for calcium

and phosphorus that they draw into themselves nearly all of the phosphorus and the calcium available in the serum. We then find a condition in which practically no urinary excretion of calcium and phosphorus occurs. Blood-phosphorus levels will be below those of hyperparathyroidism and blood-calcium levels will be below normal.

Alkaline-phosphatase levels will remain elevated or even rise to higher levels. The alkaline-phosphatase levels will remain elevated as long as the bones are hungry for mineral.

Parathyroid hormone causes the kidney to excrete phosphorus by suppression of tubular reabsorption. When the secreting adenoma is removed all available glomerular filtrate of phosphorus is reabsorbed by the tubules. However the call for this material by uncalcified osteoid is so great that for days the serum phosphorus level will be even below that of the hyperparathyroid state.

Calcium will be excreted normally in urine with decrease in parathyroid hormone. After parathyroidectomy the hungry osteoid draws so much of this element that the serum-calcium level falls. Excretion through the kidneys is reduced because the glomerular filtrate level is reduced.

Phosphorus in blood is all ionized. Calcium is not all ionized. Only the ionized form of the materials is available for matrix mineralization. The critical substance in the postoperative state is calcium. If the calcium level in blood drops to low levels tetany results. Calcium absorption is not so much of a problem. It occurs by food and mineral ingestion and is aided by the effect of vitamin D or dihydrotachysterol. The critical area is the blood; the level of calcium here must be maintained. This may be accomplished by four methods: (a) increase ingestion of calcium, (b) decrease ingestion of phosphorus, (c) increase absorption of calcium, (d) administer calcium intravenously.

It is advisable to use all of these methods in cases of hyperparathyroidism with severe

bone involvement following parathyroidectomy. The method of carrying out the above requirements is as follows:

1. Calcium rich foods, mostly milk and cheese, may be given. These foods also will supply important proteins and are high in phosphorus. The excess phosphorus may be reduced by the simultaneous administration of magnesium carbonate, strontium lactate and aluminum gel.

Calcium in the form of calcium lactate, calcium gluconate or calcium chloride should be used not dicalcium phosphate.

This regimen therefore would be: (a) milk 1 quart daily; (b) cheese preferably cottage cheese 2 to 4 ounces daily. Other foods especially fruit juices as tolerated; (c) calcium intake is fortified by 2 Gm. of calcium chloride 3 times daily for the average adult. Beware of acidosis, dehydration and indigestion. Neutral calcium compounds although less effective, may be preferable. They are the lactate and the gluconate. The dose is 4 Gm. 3 to 4 times daily.

2. To reduce the phosphorus available with the dietary sources of calcium, combine it with other materials. For this one may use magnesium carbonate, 4 to 6 Gm. daily in divided doses; strontium lactate 1 to 2 Gm. 3 to 4 times daily; or aluminum hydroxide gel 10 to 30 cc. per 100 lbs. of body weight per day roughly 20 to 60 cc. per adult per day. If it is tolerated more than one of the above may be used.

3. Vitamin D or dihydrotachysterol must be administered. Vitamin D is related to dihydrotachysterol* as 20,000 units to 0.1 mg. The purpose of this is to increase absorption of calcium from the gut and possibly to favor and maintain its deposition in bone.

Advised dosages are initially 200,000 units of vitamin D which is subsequently reduced to 10,000 units per day. The reduction is determined by following the alkaline phosphatase. When it starts to drop the vita-

* Dihydrotachysterol is marketed as Hytakerol (Winthrop-Stearns) in an oily solution in which 1 cc. = 1.25 mg. 2 capsules = 1 cc.

min D intake may be reduced to 50 000 units per day. If the phosphatase rises, the vitamin D level will have to be raised. If it continues to drop, further cut is made until finally the 10,000 units per day level is reached.

For 2 weeks at least the very high level of vitamin D ought to be maintained. After this time blood-calcium levels must also be done. If hypercalcaemia intervenes, the vitamin D intake will have to be reduced.

4. Administer calcium intravenously. This is given as the gluconate or lactate in a 10 per cent solution. One hundred cc. of 10 per cent solution in 1 000 cc. of 5 per cent glucose daily is used for severe tetany as a slow drip.

If acute tetany occurs, rapid administration of the 10 per cent solution in amounts of 10 to 20 cc. may be given. The rate of administration is 0.5 to 1 cc. per minute. Faster administration may produce brachycardia or cardiac standstill. Following this the slow intravenous drip may then be substituted.

Careful daily check-up of blood calcium, phosphorus and phosphatase is required in the first 2 weeks.

After this, weekly studies of the above must be done for another month.

Monthly x-ray studies of the skeleton should be carried out to observe filling in of bone. True cysts will not fill in; osteoclastomas will fill in.

When the alkaline phosphatase reaches normal, simple normal intake of food with normal vitamin D ingestion of 1,000 to 2,000 units per day will be adequate.

HYPOPARATHYROIDISM (PARATHYROID)

Definition. Hypoparathyroidism is a condition caused by inadequate parathyroid secretion. It results in lowered serum calcium, a tendency for condensation of bone and tetany.

Etiology. This condition may occur as a

Hypoparathyroidism (Parathyroid)

result of any damage to or removal of thyroid tissue or from actual lack of development of or hypofunction of the parathyroid gland.

The major cause is neck surgery. Parathyroid glandular tissue is either moved or damaged. In cases where the age is not permanent in type, the condition is transitory.

Cases of hypofunction of the glands have been reported as occurring idiopathically in association with moniliasis² and in conjunction with Addison's disease.³ Pathological findings¹ showed replacement of parathyroid secretory cells by fatty tissue.

Tetany of the newborn is a true hypoparathyroid state. It is due to dysfunction of the parathyroid glands at birth. The reason for the hypofunctioning glands is that those of the mother are adequate for both and as a result the glands of the fetus remain dormant.

At birth, excess phosphorus feeding results in maintained elevation of blood phosphorus levels. When a child is put upon a cow's milk formula, the symptoms are more severe than when he is breast-fed because there is relatively more phosphorus than calcium in cow's milk as compared with human milk. This secondary fetal thyroid depression will be more marked in offspring of hyperparathyroid mothers than in offspring of normal ones.

Clinical Picture. This may be divided into those symptoms and signs resulting from (a) hypocalcaemia, such as increased neuromuscular irritability and cramps, and (b) aberrant calcification.

The most prominent features of this condition are those symptoms due to hypocalcaemia, which, in order of frequency,

1. Tingling and numbness of the extremities.
2. Twitchings of the muscles that are painful.
3. Epileptiform seizures.
4. Laryngeal stridor.
5. Gastro-intestinal-tract symptoms including nausea, vomiting and diarrhoea.

6 Blurred vision probably associated with irritation of eye muscles

Signs of hypocalcemic tetany are

1 Chvostek's sign which is a tetanic hyperactive response to tapping over the point of exit of the facial nerve just anterior to the tragus

2 Trousseau's sign which is a tetanic contraction of the forearm muscles following temporary occlusion of the blood supply by a tourniquet or a blood-pressure cuff. This carpal spasm may occur spontaneously in severe cases. It is characterized by flexion of the wrist, flexion of the metacarpophalangeal joints and extension of the interphalangeal joints. A similar though not so clear-cut, contracture occurs in the feet.

3 Erb's sign which is increased excitability of the motor nerves to galvanic current. Specifically it is increased sensitivity to cathodal opening current. It differs from normal in that the threshold is below 6 milliampères.

4 Depression of the Q-T interval in the electrocardiogram

5 Laryngoscopic examination may reveal spasm of vocal cords.

6 All deep tendon reflexes are hyperirritable.

7 Electro-encephalographic tracings may reveal diffuse slow wave activity similar to that seen in certain forms of idiopathic epilepsy.

Cataract formation is seen in association with hypocalcemia and tetany in this and in other conditions such as sprue.⁴

Aberrant calcification is observed in the basal ganglia and in the cerebral hemispheres.

X-ray picture reveals that the skeleton is denser than normal. Greater deposition of calcium and phosphorus in bone is the cause. This occurs because there is decreased excretion of calcium and phosphorus as well as a decrease in osteoclastic activity.

Hypoplasia of the teeth, especially of the roots of the molars, has been reported.⁴ A clear-cut explanation of this finding remains obscure. Reduced calcification in new

forming bone areas because of reduced saturation of calcium and phosphorus from lack of parathyroid hormone may be inferred.

LABORATORY DATA. There is a lowered serum calcium both total and ionized, and an increased serum phosphorus. Calcium excretion in the urine is reduced. Phosphorus excretion may deviate little from normal. Alkaline-phosphatase levels are relatively normal. In contradistinction to tetany associated with alkalosis the phosphorus of the blood is normal. In tetany, due to alkalosis from hyperventilation, phosphorus is elevated and CO_2 combining power is reduced. In metabolic alkalosis such as that following ingestion of alkali the CO_2 combining power is elevated and the phosphorus also is elevated.

X-RAY FINDINGS. Thickening of cortical bone and metastatic calcification of soft tissues are present.

Treatment. Refer to the section on pseudohyperparathyroidism, page 195. Although hypoparathyroid cases will respond to parathyroid hormone and the pseudohypoparathyroid cases will not respond, treatment with the hormone alone is impractical. First there is danger of overdosage and hypercalcemic intoxication; second constant injection would be required; third the extract becomes progressively less effective with continuous use. This may be on the basis of the production of an antihormone or on an immune reaction.

Treatment with vitamins and chemicals as listed under pseudohyperparathyroidism, will control the symptoms.

Transplantation of fetal parathyroid glands has been done⁸ but what the long range effect may be cannot be determined with any degree of certainty.

Prognosis. This varies with the cause and extent. If temporary as in the newborn and in certain postoperative cases the condition will resolve. If of the permanent type as in event of complete extirpation of the glands or irreversible damage to them, treatment with careful control will be required indefinitely.

PSEUDOHYPOPARATHYROIDISM (PARATHYROID)

(Syn Seabright Bantam syndrome)

Historical Notes. This unusual condition was carefully described by Albright in 1942¹ At that time he reported upon 3 cases and subsequently in 1949² added 2 more cases Other authors also have reported cases of this interesting disorder^{3,4}

Clinical Features. This disease is characterized by unusual faces These people have round moonlike faces strabismus short neck, short squat build and brachydactyly

Symptoms and signs in addition to the unusual physical characteristics listed above are (a) hypocalcemia, dating from the neonatal period⁵ (b) calcification of subcutaneous tissue and of tendons (c) tetany (d) laryngeal spasm and (e) mental retardation not uncommonly this is considered due in part to cerebral edema resulting from hypocalcemia.⁶

ROENTGENOGRAPHIC FINDINGS (a) Coarse prominent bone trabeculae (b) dense cortical shadows and (c) premature closure of epiphyses especially of the metacarpals (this accounts for the brachydactyly)

PATHOGENESIS. The parathyroid glands were found to be normal¹ or hyperplastic.² Albright indicates that Cope found one case to have normal parathyroids, a second one to show expected hyperplastic parathyroids

The glands obviously are not deficient in fact they may be hyperactive in response to lowered serum calcium and probable elevated serum phosphorus. It appears that the difficulty is in the kidneys and the bones They do not respond to parathyroid hormone either endogenous or exogenous as would be expected in the normal or true hypoparathyroid. Why the end organs the kidneys and the bones do not respond is unknown

CHEMISTRY Blood-serum calcium levels are reduced blood-phosphorus levels may be elevated Urinary calcium and phosphorus excretion is reduced

Diagnosis. Clinical features plus chemical

findings clearly indicate the disorder Accurate further testing is done by the Eliworth Howard⁷ test with parathyroid hormone Following an overnight fast a moderate diuresis is induced by giving 500 cc. of water per square meter of body surface A large urine volume is maintained by subsequent administration of 200 cc. of water per cubic meter every hour during the test The bladder is emptied and then six specimens of urine are taken at hourly intervals The urinary phosphorus content of each specimen is measured After three hours and three specimens 200 units of parathyroid hormone intravenously are given to the adult and 50 units per square meter for a child

The phosphorus content of the next three hourly specimen is measured Serum phosphorus may be done concomitantly If it is desired to express their results of the test in terms of phosphorus clearance⁸ This is not necessary however

In true hypoparathyroidism or in the normal child or adult, the kidneys will react to the parathyroid hormone by reducing tubular phosphorus reabsorption This will result in definite increase in urinary phosphorus excretion in decrease of blood phosphorus and in increase in serum calcium.

In pseudohypoparathyroidism, no increased phosphorus diuresis will occur Similarly the blood-phosphorus level will not be reduced nor will the serum-calcium level be increased

Treatment. Obviously parathyroid hormone will have no effect upon this disorder A.T.10 (dihydrotachysterol) or vitamin D in large doses will produce some increase in serum calcium by increasing absorption via the gut Vitamin D in doses of 100,000 to 200,000 units daily is relatively inexpensive and less difficult to use than A.T.10 A correlation between vitamin D and A.T.10 is 20,000 units of vitamin D to 0.1 mg. of A.T.10.

Diet should be high in calcium and low in phosphorus. Accent therefore is upon milk and cheese as against seafood and

meat. Strontium and/or magnesium may also be used to combat phosphorus. Strontium lactate, 1 to 2 Gm. daily, or magnesium carbonate, 3 to 6 Gm. daily, for the average adult of approximately 150 pounds is indicated. Two thirds of this amount would be satisfactory for a 100-pound person, one half for a 75-pound patient. This rough formula should suffice to start. Magnesium or strontium combines with phosphorus and is excreted in the stool.

Talbot⁴ and Albright⁵ suggest reduction of phosphorus-containing foods, like milk and cheese, unless one is to use aluminum hydroxide in formulas. For a child Talbot recommends aluminum hydroxide gel 30 cc. per 100 lbs. of body weight per day and calcium lactate 6 Gm. per 100 lbs. of body weight per day. This would allow the normal amount of milk per day—better than 1 pint per day. The aluminum hydroxide combines with phosphorus in the foodstuff to form an insoluble complex excreted in the stool.

The above are reasonable doses of the various therapeutic agents presented here to act as a guide. They may be used singly or together depending on the case. For a brief review the agents of value are magnesium, strontium, aluminum hydroxide, calcium lactate or gluconate, or calcium chloride and vitamin D.

Accurate control is desired, however. This is achieved by daily Sulkowitch tests until the proper calcium-excretion level is reached. This is approximately a two plus value. Doses of the various therapeutic agents with the patient upon a consistent diet and vitamin D intake of 100,000 to 200,000 units per day must be varied until the proper Sulkowitch value is obtained.

Care to double check by routine serum calcium determinations is important, for hypercalcemia represents an undesirable and dangerous complication.

INTRODUCTION TO OSTEOPOROSIS

Osteoporosis is a deficiency of bone substance. It results from absorption of bone

matrix with poor replacement, from inadequate production of bone matrix or from destruction of bone matrix. Bone matrix represents the organic polypeptide intercellular connective-tissue fibers which are the product of the osteoblast. This appears to be incorporated with a mucopolysaccharide ground substance.

Many factors favor production of the bone matrix including its stimulation by androgens, estrogens and stress. Adequate protein and probably vitamin C are necessary.

This disease must be differentiated from two other conditions that also give soft bones: osteomalacia and hyperparathyroidism. Osteomalacia, which incidentally includes rickets, its childhood form, has been defined as a defect in mineralization of bone. Conversely it can also be the result of demineralization of bone. Usually, however, it is considered to be a failure of mineralization, for there is some question as to whether or not demineralization can occur without bone absorption. Hyperparathyroidism may be defined as osteoclasia or destruction of bone. This is a combination of matrix absorption and demineralization.

So frequently one's attention is drawn to an obviously softened bone on the x-ray film. It is a serious error not to consider the underlying mechanisms that can produce such a bone change. An x-ray film is only a shadowgraph which shows the relative densities of structures through which the roentgen rays have passed.

In bone, the major densities are due to the mineral elements. These elements show the nature and the configuration of the organic matrix in which they are deposited and become a part.

If reabsorption of matrix occurs, so too will reabsorption of mineral, which is a part of it, occur. This is called osteoporosis. Conversely if demineralization occurs, the residual organic matrix casts no shadow and a picture similar to that of osteoporosis occurs. Yet this condition is obviously osteomalacia.

Finally if osteoclasia and bone destruc-

tion occur without osteoclastomas, the loss of densities upon the roentgenogram is again evident. So now hyperparathyroidism has taken on the appearance of osteomalacia or osteoporosis.

To sum up postmenopausal or senile osteoporosis may resemble the bone destruction of hyperparathyroidism or the mineral deficiency present in osteomalacia. Obviously, therefore, any one of these three conditions may at times appear alike on the roentgenogram (See Table 8 p. 469).

We cannot differentiate one soft bone condition from another without taking other factors into consideration. These may be summed up as follows:

- 1 Age and sex of the patient.
- 2 Is the lesion localized or generalized?
- 3 History of the present condition including personal and family history.
- 4 Clinical examination.
- 5 Chemical studies including blood, urine, balance studies and hormone assays.
- 6 Biopsy when required and at times full autopsy examination will be the only way finally to determine the condition.
- 7 Roentgenographic skeletal survey may uncover findings in some areas that are characteristic of a disease. This would be exemplified by osteoclastomas in hyperparathyroidism, for instance.

When we consider that osteoporosis is the expression of a deficient bone matrix, many conditions producing this state in bone may be presumed.

Estrogens, androgens, vitamin C, stress and adequate protein intake are the factors known to be operative in favoring the formation of bone matrix. Any condition producing failure of one or all of these factors will result in osteoporosis.

So we have osteoporosis from the following causes:

- 1 Postmenopausal gonadal deficiency.
- 2 Senile gonadal and adrenal deficiency.
- 3 Simple disuse and post-traumatic fixation.
- 4 Destruction (a) roentgen ray and (b) supersonic.
- 5 Neurogenic.

■ Adrenal cortical hypertrophy and hypersecretion (Cushing's syndrome).

7 Malnutrition.

8 Excess protein catabolism (hyperthyroidism).

9 Deficiency in protein utilization (pancreatic and/or gastro-intestinal disease).

10 Congenital and hereditary defect in matrix formation (osteogenesis imperfecta) (Figs. 19 to 22).

11 Scurvy (vitamin-C deficiency) (Figs. 239 to 243).

12 Acromegaly (hypogonadal).

Whatever the cause, the end effect of deficient matrix is the same in the bone area involved.

It is true that in many instances osteoporosis may be generalized—for example, the postmenopausal form and Cushing's syndrome. In other instances it is localized as in Sudek's atrophy and x-ray osteoporosis.

POSTMENOPAUSAL OSTEOPOROSIS (GONADAL) AND SENILE OSTEOPOROSIS (GONADAL AND ADRENAL)

Credit for the modern identification and the handling of this entity is due largely to Albright.¹ While it is true that many clinicians had observed this rather common form of soft bones, no true understanding of this condition came about until Albright clearly defined it and thereby initiated modern methods of handling the disease.

This condition occurs primarily in women (Figs. 134 to 139 and 144 to 146). It is true that on rare occasions it has been found in men. In the instance of its occurrence in men, it has resulted from total loss of testicular function (Figs. 140 to 143). For it must be remembered that physical activity is much greater in men; therefore, their bone is not so susceptible to absorption as the bone of women. Furthermore, there is no specific relatively sudden menopause in men. The so-called climacteric period in men is a slow, gradual, long-drawn-out process.

Etiology. Matrix formation is a function



FIG. 134 (Top) Postmenopausal osteoporosis. White female 60 years old. Skull Lateral view Note the prominent diploë at the expense of normal width of the tables. All bone is involved in this generalized process. The widespread osteoporosis is more prominent in cancellous areas. As the process continues the compact bone becomes thinned



FIG. 135 (Bottom) Postmenopausal osteoporosis. (Same patient as Fig. 134) Dorsal spine. Lateral view Note the loss of trabecular detail. The bone of the vertebral bodies is barely denser than the soft tissues. Wedge compression is present in the lower thoracic vertebral bodies.

of the osteoblast. Therefore deficient numbers of osteoblasts will mean too little matrix production. The cause of osteoporosis is either too few osteoblasts or too little osteoblastic activity in matrix formation even when normal numbers of osteoblasts are present.

Matrix is primarily a protein polypeptide fiber in a mucopolysaccharide cement substance. Any deficiency of protein, excess breakdown of protein, or poor utilization of protein may result in matrix deficiency even in the presence of adequate numbers of osteoblasts.

In the postmenopausal variety, the deficiency is of estrogen production. As a result, the osteoblasts do not differentiate



FIG 136 (Top) Postmenopausal osteoporosis. (Same patient as Fig. 134.) Lumbar spine. Lateral view. Note biconcave compressions of the lumbar vertebral bodies due to the pressure of expansion of the nucleus pulposus into the less resistant softened vertebral body.

FIG 137 (Bottom) Postmenopausal osteoporosis. (Same patient as Fig. 134.) Pelvis. Anteroposterior view. Marked generalized loss of bone mineral content is to be noted. Note the denseness of the soft tissues, with which the osteoporotic bone contrasts poorly.



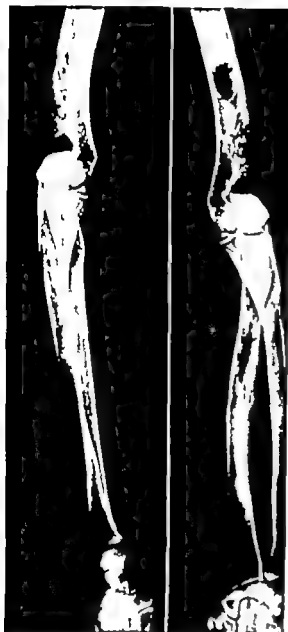


FIG 138 Postmenopausal osteoporosis. (Same patient as Fig 134) Both lower arms (forearms and wrists) showing marked osteoporosis with thinning of the cortex. In addition the porotic changes in the lower humerus contrast all the more with sharply demarcated residual bone trabeculae



FIG 139 Postmenopausal osteoporosis. (Same patient as Fig. 134) Both tibiae. Anteroposterior view. Marked osteoporosis with considerable thinning of the cortex is observed. In addition transverse infraction lines due to strain are present in the upper third of both tibiae.

into their normal numbers nor do they function fully in producing bone matrix.

The condition is more apt to occur in women who have had sudden artificially induced menopause

When menopause occurs slowly in the normal manner estrogen production does not stop suddenly and it will take up to 20 years to develop osteoporosis under these conditions. This is in sharp contrast with the condition of those suffering from artificially induced menopause in whom osteoporosis may develop to severe degree within a few years.

Clinical Characteristics The clinical findings may be divided into subjective and objective ones. The disease is found particu-



FIG 140 Postorchietomy osteoporosis. White male, 51 years old. At age 26 (1923) right orchietomy had been performed for tuberculosis, followed 1 year later by left orchietomy. By 1935 the patient had back difficulty which was intermittent. This had become increasingly severe with girdle radiations by 1947 when these original x ray pictures were taken. Serum calcium 10.2 mg. per 100 cc., serum phosphorus 3.3 mg. in 1948. Dorsal spine. Lateral view. Severe osteoporosis of all the dorsal vertebral bodies is noted. The fourth and the eighth vertebral bodies are severely wedged. Compare with similar postmenopausal findings in a female in Figure 135.

FIG 141 Postorchietomy osteoporosis. (Same patient as Fig. 140.) Lumbar spine. Lateral view. Biconcave vertebral-body compression (codfish vertebrae of Albright) is present as a result of nucleus pulposus compression of the softened bone. Note the similarity to the postmenopausal osteoporosis shown in Figure 136. In both instances, subchondral bone detail in the vertebral bodies is lost. There is almost no contrast between bones and soft tissue.

larly in women between the ages of 40 and 60. It is more apt to occur earlier in those in whom artificial menopause has been induced by surgery or radiotherapy.

Pain particularly in the back is the most consistent complaint. It may be either mild in onset with gradual increase in severity or sudden in onset accompanied by the col-

lapse of one or more vertebral bodies. Pain eventually becomes girdlelike in distribution. Often it is felt in recurrent waves of painful spasms involving the sacrospinal muscles.

Gradual loss of stature and spinal deformity with increased dorsal kyphosis occur (Figs 144 and 145). This may result eventually in a severe stooped position. Symptoms may not come on until considerable deformity has occurred but then pain may be quite severe.



FIG. 142 Postorchectomy osteoporosis. (Same patient as Fig. 140.) The patient was placed on a high protein high-calcium high phosphorus and high vitamin D intake in 1948 with combined estrogen androgen therapy as indicated in text. Dorsal spine. Lateral view (1954). Note the crisp outline of the vertebral bodies as contrasted with their washed-out appearance in Figure 140. The subchondral bone is the first to become restored in density. The patient is improved symptomatically and has discarded the Knight Taylor brace ordered in 1948.



FIG. 143 Postorchectomy osteoporosis. (Same patient as Fig. 140.) Same as Figure 142 for therapeutic program. bar spine, Lateral view (1953). bone trabecular detail is much sharper than the vertebral bodies and the sacrum compared with the pretreatment roentgenographic study of Figure 141. therapeutic program of diet vitamin D and estrogen-androgen therapy maintained indefinitely.

Pain particularly on standing, on changing position from sitting to standing or even on simply rolling over in bed may become so severe as to completely incapacitate the patient. These patients may be in severe agony of constant duration and may not become comfortable even in bed yet they may become bedfast for such a state represents the position of greatest relative comfort. Of course once a person with severe osteoporosis becomes bedfast the condition is aggravated severely because

the removal of stress favors further absorption.

The approximate weight of mineral skeleton of normal size is 6 pounds. In severe osteoporosis by the time a collapse becomes evident the loss of bone substance may be as great as 3 or more of the original 6. Obviously there will take months to years to re-establish bone substance.

CHEMISTRY Since this disease is in tissue formation, not of calcifica-



FIG. 144 Postmenopausal osteoporosis. White female, 53 years old. Dorsal spine Lateral view. Original roentgenogram taken in March 1950. Note the severe osteoporosis. This is an underexposed film with little contrast between bone and soft tissues. Compare with Figures 145 and 146.



FIG. 145 Postmenopausal osteoporosis. (Same patient as Fig. 144, now 55 years old.) Dorsal spine Lateral view. Films taken in June, 1952. Patient has now sustained wedge compressions of the seventh and the ninth thoracic vertebral bodies. She is troubled with severe back ache with girdle radiation. No hormonal and dietary treatment has been given.

Baseline chemical studies in May, 1952, revealed the following normal findings: serum calcium 9.8 mg. per 100 cc., serum phosphorus 3.6 mg., alkaline phosphatase 4.7 Bodansky units and sedimentation rate (Westergren) 2 mm. fall in 1 hour. Urinary excretion studies on Albright Reifenstein low-calcium diet were 220 mg. of calcium per 24 hours and 350 mg. of phosphorus per 24 hours. This represents increased urinary loss of both elements.

serum calcium and phosphorus are not abnormal, but the phosphorus is usually high normal. The alkaline phosphatase is normal for there is no hungry excess matrix to take up mineral.

The balance study will show a slight loss or negative balance of calcium or phosphorus in both feces and urine. The loss occurs because there is not enough matrix to allow deposit of enough mineral to produce a positive balance.

The kidneys usually are not affected, so urea is normal. 17 Ketosteroids in the postmenopausal type tend to be within normal

levels since the adrenals are still secreting nearly normal complements of hormone. Estrogen levels however are reduced.

ROENTGENOGRAPHIC FEATURES The area



FIG 146 Postmenopausal osteoporosis. (Same patient as Fig 144 now 57 years old.) She has been under treatment for 2 years with the therapeutic approach outlined in the text. High-protein, high-calcium, high-phosphorus and high-vitamin D intake have supplied the protein and the minerals necessary to rebuild the skeleton. Combined androgen-estrogen therapy has been used for its anabolic and osteoblastic effect.

Dorsal spine. Lateral view. Roentgenogram taken in March, 1954. This is a less dense film, yet note the crisp outline of the bones. The subchondral bone now sharply delineates the vertebral bodies. Symptomatic relief has accompanied the healing stage. The patient's activity has increased and now provides additional osteoblastic stimulus. Urinary-excretion studies have fallen to nearly normal levels in a test period on low-calcium diet: 140 mg. of calcium per 24 hours and 800 mg. of phosphorus per 24 hours.

showing maximum change is the axial skeleton, in particular the vertebral bodies and the pelvis. Severely advanced cases will show changes involving the total skeleton, but this is much more rare (Figs. 134 to 139).

A definite reduction in contrast of bone shadow with surrounding soft tissue is observed. The bone trabeculae in the pelvis and the spine appear fragile and thinner than normal. The over-all impression is as if the lime content of the skeleton has been washed out.

The spine shows typical changes in both the lumbar and the dorsal areas. In the lumbar areas the softened vertebral bodies allow compression of their superior and inferior surfaces from the nucleus pulposus which is under pressure. We have therefore, herniation of the nucleus pulposus into the surfaces of the bodies of the vertebrae. This produces an appearance of biconcave compression of vertebral bodies with narrowing of the vertebral bodies and with widening of the intervertebral spaces (Figs. 136, 141 and 143).

Occasionally wedge compression fractures of the anterior portions of the lumbar vertebra occur in the sudden vertebral collapse type. Often there is a progressive settling of the vertebrae or a sudden settling without wedge compression. This represents a flat type of collapse or so-called platyspondyly.

The dorsal region uniformly shows wedge compression. Since the nucleus pulposus is small there no biconcave compression occurs (Figs. 135, 140, 142 and 144 to 146).

Pathology: Gross Appearance. The changes are most severe in the spine. The vertebra may be wedge compressed as is usual in the dorsal spine or crushed as may occur anywhere in the spine (Figs. 135, 140, 142 and 144 to 146). In the lumbar area the usual picture is one of two deformities: (a) herniation of the nucleus pulposus through the end plates of the vertebral bodies to cause a Schmorl nodule. This is a cupping usually in either the upper or the lower posterior portion of the vertebrae; (b) Pressure upon the end plates on either side of the vertebral body to form a biconcave compression. This is what Albright considers to duplicate in appearance the vertebra of a codfish (Figs. 136, 141 and 143).

Section of involved bone demonstrates bone relatively easy to cut with thin relatively widely spaced trabeculations.

MICROSCOPIC EXAMINATION This shows either a paucity of osteoblasts with little matrix formation or normal numbers of osteoblasts again with little matrix. The picture shows little new bone but by staining characteristics primarily old bone.

Treatment. Reifstein and Albright² in 1947 concluded from studies on 3 cases of postmenopausal osteoporosis and 1 case of senile osteoporosis that estrogens reduced calcium and phosphorus excretion both fecal and urinary.

Some effect occurred within 6 days and persisted for 30 or more days after cessation of treatment. They used both synthetic and natural forms of estrogen and found them not too different in effect.

Serum-phosphorus levels became reduced from high normals and alkaline-phosphatase levels remained unchanged. 17 Ketosteroids were reduced.

These authors also used androgens in the treatment of these same cases. The conclusions were that similar effects occurred as with estrogens with the following exceptions:

- 1 The decrease in calcium loss required a longer time on androgen therapy to become effective and lasted a longer time than the estrogen effect after it was discontinued.

- 2 Androgens exerted a marked anabolic effect, indicated by decrease of urinary nitrogen excretion. This was not so with estrogens.

The conclusions were that a combination of androgens and estrogens would be more effective than either one alone. The authors own clinical experience confirms this and they consider that the combination allows larger doses of both androgens and estrogens with less undesirable side effects. The undesirable side effects are chiefly masculinization in the female and feminization in the male.

Huggins and Clark³ in 1940 pointed out that estrogens reduced the carcinogenic ef-

fect of androgens upon the prostate in males.

It has been the authors' practice for diagnostic purposes to place these patients upon a diet such as that recommended by Bauer and Aub⁴ or by Albright and Reifstein⁵ low in calcium and phosphorus so that the normal excretion of calcium would be expected to be approximately 100 mg per day. After 10 days on this diet total urine is collected for a 3-day period. Creatinines are done to ensure that all urine has been collected each day. Then the calcium and phosphorus output is measured. These results have indicated uniform excess excretion of both in patients suffering from osteoporosis of severe degree with clinical symptoms.

A high protein high calcium and phosphorus diet with moderate doses of vitamin D plus androgens and estrogens is given. The regimen is approximately as follows:

- 1 One quart of skim milk daily to which 20 to 30 drops of Drisdol are added. This bottle of milk must be finished each day.

- 2 Meat or seafood generous quantities at least twice daily.

- 3 Cheese preferably cottage cheese 2 to 3 ounces daily.

- 4 Eggs 1 or 2 as desired.

- 5 At least 1 green vegetable daily.

- 6 Fruit juice 6 to 8 ounces any kind daily.

Any other foods if the patient desires them.

MEDICATIONS

- 1 A standard preparation of vitamin D like Drisdol without vitamin A (Winthrop-Stearns) 20 to 30 drops in milk daily.

- 2 Multivitamin capsule 1 daily.

- 3 Aqueous testosterone by injection 50 mg daily for 3 days thrice weekly for 1 week twice weekly for 1 week. Then 25 mg 3 times weekly thereafter. Maintenance androgen dose does not usually exceed 300 mg per month. This may be given by injection. The authors prefer to give this as testosterone 10 mg per day transmucosally or in combination with estrogens (see below).

- 4 Conjugated estrogens (Premarin—

Ayerst McKenna and Harrison) 1.25 mg t.i.d. for the first 28 days. Estradiol U.S.P. same dosage. Since ethinyl estradiol has 25 to 50 times the potency of the above the dose is only 0.05 mg 3 times daily.

The primary estrogens estradiol estrone and estriol are mainly destroyed when taken by mouth apparently by the stomach and the liver they must be taken transmucosally or given parenterally.

Conjugated estrogens and ethinyl estradiol are not affected appreciably when taken orally.

It is the authors policy to use the major concentrations of androgens and estrogens within the first month. This is done in order to more rapidly combat the symptoms presented by the patient. Furthermore within the first month undesired virilizing or feminizing effects are not so likely despite the large quantities of hormones given.

After 28 days the more acute symptoms are usually relieved materially.

5 Thereafter administration of hormones is as follows. Ethinyl estradiol 0.05 to 0.1 mg daily (oral). Testosterone 10 mg daily (transmucosal).

One may substitute Premarin 1.25 mg (oral) or estradiol 10 mg (transmucosal) once to twice daily for the ethinyl estradiol.

Prognosis. Although this disease is primarily a lack of organic matrix its degree is reflected in the mineral picture. These cases may demonstrate a loss of one half to two thirds of the total body minerals.

Replacement of the minerals will require a very long time. To replace them infers first manufacture of matrix and later its calcification.

It is reasonable to presume that protein is necessary for matrix formation just as stress and gonadal hormones are necessary to stimulate the manufacture of matrix. So too are calcium phosphorus and vitamin D required to have material to enter into calcified matrix formation. Finally, every possible physical activity must be urged to stimulate bone formation.

On an ideal high protein calcium phos-

phorus vitamin and gonadal intake the maximum retention will not exceed 2 Gm. of calcium per day. Therefore to replace 2 or more pounds will require 1 000 days (Figs 140 to 146).

Patients with this disease must understand that they have to be patient and that they must follow directions implicitly. They must be warned of untoward side-effects. If these occur the hormone at fault must be reduced. When a patient is bedfast and treatment is instituted every possible effort must be made to increase physical activity and large amounts of fluids must be used to obviate kidney-stone formation.

With care excellent results will be obtained. The initial test diet should be used as a baseline study before instituting treatment. The serum phosphorus and calcium and urinary excretions of these minerals should be checked periodically during treatment. Many bedfast pain racked persons have very quickly become ambulatory relatively pain free and able to work again.

Since this condition is expected inevitably to develop in women possibly the best treatment is prevention. So exercise a good diet high in protein minerals and vitamins plus small doses of hormones might be started at the outset of the menopause.

CUSHING'S SYNDROME (ADRENAL)

History. The eponymic title of this disease entity is related to the original concept of its being based upon a primary pituitary basophilism.¹ The hyaline changes in the basophile cells of the anterior pituitary² today are considered to be secondary in nature to a primary hyperadrenocorticism.

About one third of the cases reported appear to result from a unilateral adrenocortical carcinoma. Most of the remaining cases manifest bilateral adrenocortical hyperplasia. Some cases on exploration present normal biopsy material of the adrenal cortex. Almost all cases of Cushing's syndrome will manifest the aforementioned hyaline



FIG 147 Cushing's syndrome (Figs. 147 to 151 from Dr Eugene P. Pendergrass) Large adrenal adenoma found and resected. Patient died of acute adrenal insufficiency. Rib cage and dorsolumbar spine. Anteroposterior view. There is definite osteoporosis with loss of bone trabecular details. Note the minimal amount of contrast between the soft tissues and the bones.



FIG 148 Cushing's syndrome (Same patient as Fig 147) Lumbar spine and pelvis. Anteroposterior view. Bone cancellous trabeculae are almost completely "washed out." Some subchondral bone is seen at stress points like the acetabular roof, the femoral calcar, and the linea terminalis of the pelvis.

changes in the basophilic cells of the anterior pituitary as described by Crooke.²

Just under half of the cases with adrenocortical hyperplasia will, however, present a basophilic adenoma of the pituitary. The interrelationship of the pituitary gland to the adrenal cortex in these cases is not definitely clear. The syndrome does occur in primary adrenal-cortical carcinoma cases with only hyaline Crooke's changes but without pituitary adenoma. This would indicate that the adrenal cortex in many of the cases is the primary cause. However, the syndrome can and probably does result from pituitary adenoma.

Clinical Symptoms. Cushing's syndrome presents a typical type of physical habitus. There is a peculiar type of obesity manifested by large amounts of fat deposited in the trunk, mooning of the face, a "buffalo

hump" at the base of the neck, and rather thin upper and lower extremities. There is a marked plethora of the face and also a dusky tinge to the skin of the rest of the body. The skin is also subject to easy bruising and the formation of striae. There is hirsutism without any other manifestation of virilism. Muscular weakness is very extreme and occurs in 9 out of 10 cases. Hypertension is severe and affects both the systolic and the diastolic components of the blood pressure.

In adolescent and adult females amenorrhea is very common. Impotence is seen in males afflicted with this syndrome. A derangement of carbohydrate metabolism is present, with hyperglycemia, glycosuria and acetoneuria being found. This diabetic state is resistant to insulin therapy.

The adrenal-cortical carcinoma in those



FIG 149 Cushing's syndrome. (Same patient as Fig 147) Dorsal spine. Lateral view. This is a very light film with minimal contrast between bone and soft tissues. Note the poor trabecular detail of the vertebral bodies. Wedge compression of the body of the eighth thoracic vertebra is seen.



FIG 150 Cushing's syndrome. (Same patient as Fig 147) Lumbar spine. Lateral view. Severe osteoporosis is present. Compression of the lumbar bodies has occurred. Biconcave intervertebral disk expansion into the softened bone has occurred.

cases where it is the cause of the syndrome may of course cause symptoms of local expansion and metastasis with fatal termination.

Our primary concern with this peculiar disease state lies in its bone changes. In the adult these are represented by a severe osteoporosis (Figs 147 to 151). In children there may be osteoporosis and premature cessation of epiphyseal growth.

PATHOLOGIC PHYSIOLOGY It will be recalled that two separate types of hormonal secretions originate in the adrenal cortex. In terms of the steroid nucleus the basic difference is that the so-called sodium potassium hormonal component has an oxygen at carbon 11 and is called 11-desoxy

corticosterone. This hormone is relatively unimportant in the pathogenesis of Cushing's syndrome which has only minimal electrolyte disturbances.

The second adrenocortical hormone type is the S-FN (or sugar fat nitrogen) hormone group. These are sometimes designated as 11-17-oxycorticosteroids because of the presence of oxygen at the 11 and 17 carbon atoms in the steroid nucleus. Albright believes that the mechanism of this S-FN group of hormones in the body is a dual one.²

The N hormone is considered to be an

Fig. 151 Cushing's syndrome (Same patient as Fig. 147) Forearm and hand Anteroposterior view. Similar but less marked osteoporotic changes have affected even the limb bones. The coarsening of trabecular structure almost resembles the roentgenographic appearance of osteitis fibrosa cystica in hyperparathyroidism. The contrast between the medullary cavity and the cortex is well preserved in this example of osteoporosis. Contrast with Figure 118.



anabolic one stimulating osteogenesis and causing rapid growth early in life. It also causes premature closure of the epiphysis as is seen in the adrenogenital syndrome.

The "S" hormone is considered to be anti-anabolic rather than catabolic. There is thus a fundamental antagonism between the "S" and the "A" hormones.

The mechanism particularly of osteoporosis is explained on the action of excess "S" hormone on an anti-anabolic basis. The difficulty is felt to be retardation of osteoblastic function with a reduction in the quantity of matrix formed. The purely catabolic reaction would be an osteoclastic one such as is seen in hyperparathyroidism.⁴

LABORATORY FINDINGS. There is a fall in the total and the relative amounts of eosinophilic leukocytes in the blood. About a third of the cases have polycythemia. Diagnostic urinary steroid studies reveal abnormally elevated quantities of 11-17-oxycorticosteroids, while urinary 17-ketosteroids are within normal limits or only slightly elevated. If there be any marked component of the adrenocortical masculinizing symptoms the 17-ketosteroids will be elevated. Some cases have a mild disturbance of electrolyte findings. There is a tendency to hyponatremia, elevated plasma bicarbonate and an associated hypokalemia and hypochloremia.

A mild negative nitrogen balance is present which will not respond to excess food intake. Patients show an increased excretion of calcium and phosphorus in the urine but the serum calcium and phosphorus values are normal. Alkaline phosphatase is normal but will become elevated during the

stage of healing as the calcium balance becomes positive.

RADIOLOGIC FINDINGS. Diagnosis of the adrenal neoplasm may of course be aided considerably by perirenal air insufflation. Renal pyelography usually retrograde may be of further assistance. In addition to the usual radiographic studies for metastatic neoplasm may be indicated in certain cases.

The particular finding of interest is the

presence of osteoporosis of characteristic type in the spine (Figs 147 to 150) There is definite biconcavity of the end plates of the adjacent vertebrae in the lumbar spine, evidence of collapse may be seen in the thoracic spine Nuclear extrusions of the Schmorl type may be seen Collapse may be so extreme that intervertebral foramen narrowing with impingement on nerve roots may be correlated with clinical symptoms of girdle pain.

The radiographic evidence of healing is evidenced by the deposition of bone in the thoracic and the lumbar regions of the spine In children with this entity the deposition of cortical bone at the end plates of the vertebrae is particularly marked when healing occurs

Roentgenographic studies of the kidneys may reveal nephrocalcinosis or nephrolithiasis secondary to the excess calcium and phosphorus excretion

Treatment. This depends partly on the success in determining the primary adrenal causation It may be produced by a benign adrenal tumor Those patients with Cushing's syndrome resulting from adrenal cortical carcinoma may die of metastases because resection has been unavailing

In those cases where bilateral adrenal hyperplasia is found subtotal adrenal resection² has been carried out. Unfortunately the after effects of this type of surgery in Cushing's syndrome have been associated in the experience of those who followed these cases with an acute hypo-adrenocorticism.

Pituitary irradiation was used originally before the adrenal-cortical etiology was thoroughly worked out Dosage was 2 000 to 3 000 roentgen units It is now reserved for cases where no adrenal-cortical carcinoma has been found on exploration or where bilateral subtotal adrenalectomy has failed to relieve symptoms or to prevent their recurrence after a remission

In cases of the hyperplastic rather than the malignant type symptoms may still persist despite resection and even radiotherapy

Some cases remit and then recur following these therapeutic measures

The best therapy available at present writing for the resistant or recurrent type of case is the use of testosterone which is considered to be an 'N' hormone and therefore antagonistic to the action of the oversecreted 'S' hormone Testosterone may also have some value in retarding the pituitary secretion of adrenocorticotropin.

With testosterone therapy negative nitrogen calcium and phosphorus balances are reversed There is an elevation of alkaline phosphatase in response to the healing of the osteoporotic condition Estrogen therapy may also be used for its specific effect in complementing testosterone and avoiding secondary masculinizing effects Estrogen, it is to be remembered has a specific effect on retention of calcium by stimulating bone deposition

Prognosis. The prognosis in this syndrome is poor Cases resulting from adrenal-cortex malignancy have in addition to the secreting tumor the prognosis of the carcinoma itself which is poor because of failure of early recognition and tendency to spread Those with metabolic disturbances only from adrenal-cortical hyperplasia or perhaps the postulated pituitary adenoma etiology have severe sequelae particularly in relation to hypertension with its effect on the peripheral vascular and cardiac systems.

HYPERTHYROIDISM (THYROID)

It is not certain that hyperthyroidism per se produces appreciable bone changes. However Aub¹ reported increased calcium excretion in feces and urine in hyperthyroidism and decreased excretion of calcium in myxedema.

A loss of protein probably due to excess catabolism is associated with this disease Administration of testosterone increases the nitrogen balance and decreases urinary calcium excretion² Osteoporosis has been reported and may occur in association with the protein and calcium loss.

The usual clinical manifestations of this disease are well known they are not discussed in detail here

In growing individuals or children a toxic thyroid state can interfere with growth because of the marked protein depletion in association with the loss of calcium

The chemical findings may be summed up as follows

- 1 Normal or lowered cholesterol
- 2 Basal metabolic rate usually increased although normal metabolic rates have been reported in hyperthyroid people
- 3 Increase in PBI (protein bound iodine)
- 4 Increase in thyroid uptake of iodine¹³¹
- 5 Increase in calcium excretion through the urine
- 6 Increase in nitrogen excretion through the urine
- 7 Creatine values in the urine increased to above normal levels
- 8 Increase in protein bound serum magnesium

The cholesterol is primarily of value in following response to therapy in hyperthyroidism This means that adequate therapy will result in an increase in the blood cholesterol above the level maintained prior to treatment. At times prior to treatment the cholesterol level may be normal and a proper response to treatment will result in a higher cholesterol level

PBI or protein-bound iodine has a normal value of 4 to 6 micrograms per cent In hyperthyroidism it is above 6 When the level is below 4 one may presume the condition to be hypothyroid The PBI differentiates hypermetabolism from hyperthyroidism. We may place under hypermetabolism such conditions as leukemia polycythemia Hodgkin's disease and infectious conditions

Tracer studies involve administration of between 40 and 100 microcuries of radioactive iodine The urinary excretion is determined in 24 to 48 hours. The urinary excretion of radioactive iodine is reduced in the hyperthyroid state because the hyper

active thyroid takes up more radioactive iodine than the normal one The extra radioactive iodine therefore would show in the thyroid gland and less radioactive iodine would appear in the urine

A Geiger counter is used to measure the radioactivity of the thyroid When 10 to 35 per cent of the ingested dose is observed over the thyroid in 24 hours after administration that is considered to be normal Above that amount would indicate the presence of hyperthyroidism.

In the urine the measurement would be indicated by 20 per cent or less as consistent with hyperthyroidism 21 to 35 per cent would be considered borderline 35 per cent definitely in the normal range

Creatine is not usually found in the urine in males It is found in some females normally In adults it is either absent from the urine or is present in amounts of less than 40 mg in a 24-hour specimen. Women have it during menstruation gestation and lactation and both sexes show it in starvation or following very high protein diets

Creatinine is a degradation product of creatine and is found in the urine between 12 and 17 Gm. per day It is quite consistent in individuals and is used to check the volume of 24 hour urine specimens.

Richardson and Shorr³ in 1935 developed a creatine tolerance test When an individual is on a creatine-free diet and then is given a fixed amount of creatine a great deal was put out in the urine in hyperthyroid individuals The creatine storage capacity of the muscles is impaired in hyperthyroidism Spontaneous creatinuria is seen in muscular dystrophies and muscular atrophies.

Magnesium Partition Studies. In hyperthyroidism there is a considerable increase in the percentage of protein-bound magnesium in the serum.⁴ In the normal the percentage is 10 to 20 and in hyperthyroidism is above 25 This is not associated with change in total serum magnesium concentration After Lugol's solution is given, this serum bound magnesium returns to lower

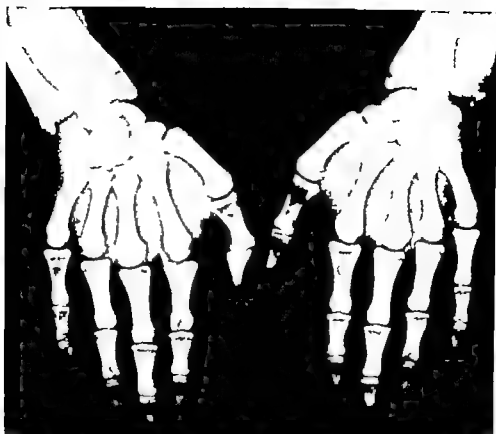


FIG 156 Hypothyroidism (Same patient as Fig 154) Both hands and wrists. Anteroposterior view. The bones are broad and short. The distal tufts are very small. Note the residual epiphyseal cartilage plates in radius, ulna, metacarpals and phalanges bilaterally.



FIG 157 Hypothyroidism. (Same patient as Fig 154) Pelvis. Anteroposterior view. Bilateral coxa vara. The deformity is secondary to osteochondritis with fragmentation of the femoral heads and short thick femoral necks.



FIG 158 Hypothyroidism (Same patient as Fig 154) Both feet and ankles. Oblique view The opposing talotibial articular surfaces are flattened. A similar abnormal configuration can be seen at the posterior talocalcaneal articular facet. Note the transverse lines of arrested growth in the distal tibia. Similar lines were present around the knee joint.

Teeth are susceptible to caries and deciduous dentition is delayed if hypothyroidism occurs early in life. The position and the shape of teeth when they do erupt are irregular.

Looser¹ described retardation in the transformation of cartilage into bone at the epiphyses.

Diagnosis. Hypothyroidism in infancy may be suspected on the clinical basis if the following findings are evident: the patient may be somewhat heavy, although apparently of average size. He will feed poorly and is rather slow in movement. His head appears large with wide-open anterior fontanelles.



FIG 159 Hypothyroidism (Same patient as Fig 154) Both feet. Anteroposterior view. The bones are shortened and delicate for an adult male. As in the hands the distal phalangeal tufts are greatly reduced in size.



FIG 160 Gigantism. (Figs. 160 to 162 from Dr. Eugene P. Pendergrass) White male 13 years old. Height 6'5" (7" growth in last 8 months). Weight 150 lbs. Undescended testes with normal secondary sex characteristics. No acromegalic characteristics. Work up negative for pituitary eosinophilic adenoma. In this case, gigantism is probably physiologic but possibly hypogonadal in etiology. Pelvis: Anteroposterior view. Bones tremendously enlarged in size but well proportioned. Capital femoral epiphyses overdeveloped for patient's age.

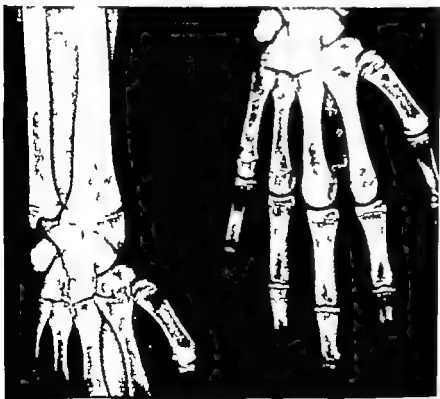


FIG 161 Gigantism. (Same patient as Fig. 160.) Right hand, wrist and forearm. Anteroposterior view. There is overgrowth of all the bones in symmetrical fashion. The finger tufts are not overgrown as in acromegaly. Epiphyseal ossification is accelerated throughout the wrist and the hand.

tels and frontal sutures. His skin may appear dry and scaly. His eyelids are thickened so that the palpebral fissure appears narrow but the fissures will be horizontal rather than oblique as occurs in mongolism. His abdomen will be protuberant. His tongue thick and enlarged and there is retardation of dentition and weight gain as in general growth in length.

LABORATORY AIDS. X-ray picture will reveal that the lower end of the femoral and the upper end of the tibial epiphyses which should be present at birth are absent. The wrist at 6 months of age should show the capitate and the hamate and at 1 year the distal epiphysis of the radius is present; at least 90 per cent of normal children (Figs. 152-153). Following this the carpal bones appear approximately 1 per year.

OTHER LABORATORY FINDINGS. Cholesterol is elevated although at times it may be within normal ranges. No matter what the level when the test of thyroid administration is carried out the serum cholesterol shows a distinct fall of at least 100 mg.

The protein bound iodine level is lowered and is usually less than 2 micrograms per 100 cc., rarely exceeding 4 micrograms per 100 cc. of blood. Thyroid uptake is reduced.

The radioactive iodine uptake by the thyroid gland is not so satisfactory as PBI determination but will show an absence of uptake or a marked decrease of I_{131} . Conversely the urine will show an increase in the 24- to 48 hour excretion of radioactive iodine.

Basal metabolic rates are too difficult and impractical in infants.

Creatine excretion is below normal limits but following the administration of thyroid hormone creatinuria will occur to normal levels. When there is no thyroid gland present, then thyrotropic hormone will produce no creatinuria for there would be no thyroid gland to activate.*

The serum alkaline phosphatase is often decreased.² The serum alkaline phosphatase is less than 4.5 to 5 Bodansky units. This is evidence of pathology of epiphyseal changes. The serum carotene level is often increased in hypothyroidism.⁸ This is presumed to occur because of the inability of the liver to convert carotene to vitamin A. Hypercarotenemia is also found in other liver diseases. In Cushing's syndrome and after eating food containing large amounts of carotene. Hypolipemia is another consistent finding in childhood hypothyroidism.

DIABETES MELLITUS (PANCREAS)

Osteoporosis has been observed not infrequently in advanced cases of diabetes mellitus. A precise correlation is not proved. It may be as Albright¹ suggests that it results simply from prolonged use of protein for energy and that excess protein catabolism then depletes the protein needed for bone matrix formation.

It is also to be borne in mind that many cases of osteoporosis in this disease are probably of postmenopausal or senile type.

Therefore the osteoporosis would simply be coincidental to the diabetes.

It is of interest also that osteoporosis of the bones of the hands and the feet is noted with incipient or actual arteriosclerotic gangrene.² This type frequently accompanies diabetes. Here the mechanism is clearly circulatory.

Generalized osteoporosis however although observed as indicated above cannot be related clearly or consistently to diabetes mellitus.

GIGANTISM (PITUITARY)

Definition. Gigantism is a condition in which there is excessive skeletal growth in a symmetric manner far in excess of the average for persons of that same race and which is due to excess secretion of pituitary growth hormone (Figs. 160 to 162). Furthermore this condition must have its onset in hypersecretion of pituitary growth hormone prior to the closure of the epiphyseal plates. Once the epiphyseal plates have closed normal linear growth no longer can occur and then excess growth resulting from too much growth hormone will be manifested in the flat bones the digits with tufting of the fingers and the other characteristics that are typical of acromegaly (Figs. 171 to 174). Pituitary giants are well proportioned.

It must be borne in mind that individuals of large stature can also occur from another condition strongly approximating some of the characteristics of primary pituitary gigantism. This is primary eunuchoidism which refers to the condition of those individuals who have no gonadal secretion because of removal of the gonads by surgery their destruction by trauma or disease or gonadal atrophy such as accompanies cryptorchidism. Theoretically the female could also be an individual suffering from primary eunuchoid gigantism except for the fact that her gonads are less susceptible to injury. The ovaries function within the abdominal cavity and do not undergo a syndrome comparable with that of male cryptorchidism.



FIG. 162 Gigantism (Same patient as Fig. 160) Skull. Lateral view. The vault is small compared with overgrowth of the rest of the skeleton shown in Figures 160 and 161. The sella turcica is normal, but there is calcification above it.

In eunuchoid gigantism therefore growth of symmetric type occurs if the gonads have been destroyed before sealing has occurred and then of course the growth is excessive due to the fact that the epiphyseal plates persist for an inordinately long time. Growth of individuals suffering from eunuchoid gigantism may be quite great, approximating that of the smaller primary hypophyseal giants.

Primary eunuchoid gigantism is characterized on laboratory findings by an excess excretion of pituitary gonadotropins. The reason is that since the gonads are not functioning the pituitary puts out an ever increasing amount of gonadotropins which still do not produce gonadal function. This continues until the pituitary becomes exhausted with the development of foam or castration cells.

Pituitary giants usually have low gonadotropins. This is probably due to encroach-

ment upon the rest of the gland by the tumor.

Historical Notes. This disease is not a common one yet it has occurred throughout human history. As a result in the early as well as the later writings of every country one finds accounts of people of gigantic proportions.

In Greek mythology from the blood of Uranus wounded by his son the Titan Cronus there sprang a race of giants. According to Homer there was a race of gigantic and savage men dwelling in the island of Triacria. Orestes according to the Greeks was nearly 10 feet tall. The belief in giants was part of the everyday life of the ancient Greeks and Romans. They even represented them in their pottery. Homer told in the *Odyssey* how Ulysses blinded the gigantic Polyphemus even more familiar is the Bible story of David and the 9 foot Philistine Goliath.

Pliny held that in the beginning man was gigantic

Giants are mentioned half a dozen times in the Old Testament notably in Genesis Deuteronomy Joshua Numbers Samuel and Chronicles. In the Bible there are many references to men of enormous stature. Such men are first written of in Genesis VI 4 under the name of Nephilim as follows:

"There were giants in earth in those days." In Numbers 13:33 "And there we saw the giants the sons of Anak which come of the giants and we were in our own sight as grasshoppers and so we were in their sight."

The next race of giants mentioned in the Bible are the Rephaim of whom the earliest record is in Genesis 14:5 where we are told that Chedorlaomer and some allied kings defeated them at the Ashteroth Karnaim. Goliath the famous giant of Gath the champion of the Philistines whom David slew was in height (according to 1 Samuel 17:4) 6 cubits and a span. Assuming the cubit to be the cubit of a man this would make him 9 feet 9 inches tall and if a cubit was 21 inches it would make him about 11 feet, 5 inches tall. Josephus however gives his height as four cubits and a span and describes him as a truly enormous man.

John Bunyan in his immortal work tells of the pilgrim's progress and how Christian meets Giant Pagan and Giant Despair.

Modern scientific description of hyperpituitarism begins with Pierre Marie¹ (1886) who reported 2 cases which he termed acromegaly. Minkowski² (1887) related gigantism and acromegaly as diseases of the pituitary gland. Brissaud and Meige³ (1895) believed that gigantism is acromegaly during the period of growth and that acromegaly is gigantism in the adult. According to Cushing (1910)⁴ acromegaly was caused by an overproduction of qualitatively normal secretion of the eosinophile cells of the anterior part of the pituitary gland.

In 1921 Evans and Long⁵ produced gigantism in the rat by injection of anterior pituitary extract.

Incidence. Gigantism is a relatively rare condition. One of the tallest giants recorded in literature outside of folklore or mythology was John Middleton the Kentucky or Mitter giant⁶ described in a report concerning 31 true giants ranging in height from 7 feet 6 inches to J M. who was 9 feet 3 inches.

In general pituitary gigantism is not familial. Humbert⁷ doubted that any giants were much over 8 feet 3 inches. He cited the Alton giant as actually measuring 8 feet 3¼ inches at the age of 18.

Etiology. Pituitary gigantism is due simply to excess growth hormone production by the pituitary. Selye⁸ refers to this hormone as somatotrophin. This condition usually is associated with a tumor of eosinophilic cells of the anterior hypophysis. It also may be due simply to hyperplasia of the anterior hypophysis or to carcinoma involving the pituitary gland. With increased growth or the increased size of the anterior pituitary enlargement of the sella turcica occurs. In addition encroachment upon other portions of the pituitary gland by the adenomatous or the hyperplastic anterior pituitary may well result in reduction in the elaboration of hormones by the rest of the gland. Therefore it is not uncommon to find reduction in gonadotropins for instance in this type of gigantism.

Excess anterior pituitary growth hormone will then with the reduction of gonadotropins in particular cause continued and extra rapid growth in all epiphyseal areas and this growth will continue to a time far beyond the normal time for sealing of the epiphyseal plates. It has been not uncommon to find epiphyseal plates open at the age of 25 years or more. Obviously as the centers are not sealed and there is a longer time for growth to occur and a stimulation for growth continues the amount of growth is also increased markedly.

With the excess amount of growth hormone elaborated there also appears to be a greater amount of growth per unit of time. It is primarily this factor that leads to the

major gigantism. Most pituitary giants have attained nearly complete growth by the age of 18.

Clinical Features: SIGNS AND SYMPTOMS. The signs are those of a general symmetric overgrowth of the body. The length of the body and the size of the viscera exceed average measurements. A person may attain a height varying from 6 feet 8 inches to above 8 feet.

Rapidity of growth is usually noted in childhood but may be most conspicuous during adolescence. Acromegalic manifestations occur in some giants—those in whom the hyperfunction of the pituitary continued after epiphyseal union.

Sexual development and libido may be normal or even supernormal at first, but after some years impotence and lack of primary and secondary characteristics usually develop. Visceral enlargement occurs but is proportionate to body size. In acromegaly the enlargement of the viscera is excessive in relation to body size.

These individuals usually have visual difficulties manifested by bitemporal hemianopsia. They are described usually as being physically strong and mentally alert. As in acromegaly but not so often sometimes the complication of hyperthyroidism and diabetes mellitus is present. There are frequently intracranial symptoms of headache. Round shoulders are quite common.

Trophic changes may be apparent in the feet of giants usually manifested as ulcers and a tendency toward infection. This may be explained by the fact that there could be excess stretching of either vessels or nerves because of excess body growth. The hands are particularly diagnostic in that they are very large and bony. Muscular development is not usually increased to the same degree as skeletal growth. Later in the disease these people are weaker than their size would indicate.

The delayed epiphyseal closure usually is associated with decrease in gonadotropic hormone and probably would indicate an invasive type of pituitary tumor.

The pituitary may burn out here as it

may in acromegaly so that there is transition to hypopituitarism and ency toward cachexia and senile, excessive senility for the age. Reported irregular ossification and epinecrosis.

LABORATORY DATA. There is often a reduction of pituitary gonadotropins. Ketosteroid urinary excretion is usually slightly reduced. Occasionally diabetes and hyperthyroidism may occur. Confirmatory laboratory data.

Röntgenographic Features. Symmetric enlargement of the system is found (Figs 160 to 162). Of the sella turcica may be noted a delay of fusion of epiphysis occasionally when gonadotropin is deficient. Ossification appearance of ossification epiphyseal plates may be very late, coming sometimes past the age of 20, but rule however epiphyseal closure was at approximately the normal time.

When the acromegalic phase occurs following are apparent: (1) prognathism; (2) enlargement of the frontal sinus; (3) tufting of the distal phalanges; (4) tufting of the metacarpals; (5) enlargement of the metatarsals; (6) hypertrophy of the soft tissues.

Pathology: Gross Appearance. Microscopically the pituitary gland may be either normal or enlarged. If there is an increase in the size of the anterior pituitary. The enlargement is great enough to erode the sella. Except for size the skeleton itself pathologic in structure.

Microscopic Appearance. Microscopically tiny or large adenomas may be present. There is usually a preponderance of eosinophilic cells. There may also be mixed-cell adenoma which combine eosinophils and basophils.

Differential Diagnosis. Pituitary tumor must be differentiated from eugigantism and primordial constitutional gigantism. This latter is the familial type and these people are normal.

Treatment. Hurxthal¹⁰ believed that

gical treatment is in order with removal of the pituitary adenomas. Roentgen therapy, at times appears to slow the process by reducing eosinophile cell secretion.

Testosterone may be used in an effort to cause early epiphyseal closure. It may cause an initial increase in growth but this should be followed by sealing of the epiphyseal plates and consequent cessation or retardation of growth. It should be remembered that while this may halt linear growth acromegalic type overgrowth may still occur.

FIG 163 Pituitary dwarfism (From Dr Eugene P Pendergrass) Note the small stature as compared with the yardstick the patient is holding. There is fairly good muscle development in this case. (Bottom left) Lower arm, forearm and hand leg. Anteroposterior views. The long bones are reduced in length. There are definite growth abnormalities in the distal radius the ulna, the tibia and the fibula. The progressive acral shortening of the phalanges suggests a hypothyroid component in this entity. Compare with Figure 156 (Bottom right) Lumbar spine and pelvis. Anteroposterior view. Note the small delicate skeletal structures. The hip joints show acetabular shallowness and deformity of the femoral heads and necks. The latter is more marked on the right than on the left. Compare with the hypothyroid pelvis of Figure 157.



secondary to the hypophyseal somatotrophic oversecretion. The dosage recommended¹¹ is 50 mg of testosterone administered intramuscularly 3 times a week for 4 weeks. The course is repeated at intervals of 4 to 6 weeks until epiphyseal closure has taken place.

In a female afflicted with this disease it may be more appropriate to use estrogens to induce epiphyseal closure. The daily oral use of 5 to 10 mg of diethylstilbestrol for 20 consecutive days out of every month has been employed.¹²

It should of course be recalled that pituitary gigantism is much more common in males than females and that consequently this latter therapy is rarely indicated. As in the instance of testosterone the female sex hormone will merely produce epiphyseal union and will not affect the acromegalic overgrowth of the pituitary growth hormone.

Prognosis. The prognosis for life is poor. These individuals tend to be susceptible to and succumb to infection. Only a few go on to middle life.

DWARFISM (PITUITARY)

Definition. A dwarf is a person whose physical dimensions are markedly less than those characteristic of his age, sex, group and race. The usual dwarf, aside from the primordial one, is of the hypopituitary type (Fig. 163).

Variation in stature does occur in *cretinism*, in *osteogenesis imperfecta* and in rickets of the gastro-intestinal, the pancreatic, the renal and the vitamin D resistant types. It is observed also in ovarian agenesis (Turner's syndrome). However the prime concern here is dwarfism related to pituitary dysfunction.

Historical Notes. Legends concerning a race of people of abnormally small stature have been common in all parts of the world from an early period of history. Homer referred to pygmies who were believed to be found in Thrace and Herodotus wrote of a people of extremely small stature who dwelt

in the Libyan deserts. It is noteworthy that the Bible, which makes such frequent mention of giants, names a dwarf only once—in Leviticus 21:20, where it is commanded that no dwarf shall make the offering at the altar. This was an edict true for all mutilated persons.

The custom of having dwarfs and deformed men in the suites of grand personages was common in the East from time immemorial. Dwarfs were popular with wealthy Romans who kept them for diversion. Most of these dwarfs came from Egypt and Syria.

In 1871 Loran and de la Cour¹ described a group of tuberculous persons in whom they noted arrested skeletal and genital development. They termed the condition *fantillism*. Mistakenly a misquoted version of their paper was included in the literature as "dwarfism" and "infantillism" and Loran's name was identified with a syndrome which was not exactly the condition he and his pupil had described. It was widely believed that the Loran dwarf had the body proportions of an adult in miniature. In effect, what these men really wrote was that their tuberculous patients were juvenile in appearance and persistently infantile in somatic and sexual development, despite advancing years. It is quite possible that the arrested development in these cases were simply the result of malnutrition and chronic tuberculosis. It was not until 1908 that Lévi described true primary hypopituitary dwarfism with hypogonadism. Nevertheless, the term Loran-Lévi is given to this type of dwarf.

Simmonds² described hypophyseal cahechia in 1914. Although he referred primarily to that state following postpartum hemorrhage,⁴ it is seen in males and female patients suffering from a variety of other causes. These include pituitary tumors, tuberculosis, luetic gummata and trauma with hemorrhage about the pituitary. Furthermore, if hypophyseal destruction occurs in childhood, dwarfism will result.

Incidence. Dwarfism is uncommon. The

primordial type or the pygmy is not an endocrine dwarf. Pygmies are found especially in central Africa and in the Amazon forests.

Etiology. Hypopituitary dwarfism is the result of destruction of the anterior lobe of the hypophysis. The causes may be many, the principal one being a tumor, usually a craniopharyngioma or a chromophobe adenoma. These tumors secrete no hormones but destroy tissues that normally do secrete hormones.

Hypopituitarism may occur with tumors of the hypothalamus as in the form associated with Froehlich's syndrome (dys trophia adiposogenitalis). Most Froehlich cases do not present a full hypopituitarism but only a deficiency of gonadotropin. Thus they may be normal or excess in size.

Decreased pituitary secretion resulting in dwarfism also occurs as a result of a non-specific atrophy of the gland or because of destruction by tuberculosis or syphilis. Trauma with hemorrhage about the gland may cause early pituitary destruction but is more common in the late or Simmonds type of anterior lobe disease.

Clinical Features. Hypophyseal dwarfism is symmetric and well proportioned. There is a proportionate diminution in the size of the trunk and the extremities. The hands and the feet are small and delicate. The head is extremely small and the features are childish. With increasing age the facial skin tends to become atrophic and wrinkled at a relatively early age (Fig. 163).

The intellect of the hypophyseal dwarf is good but there is great emotional instability. This may be due to a large degree to hypogonitalism and sexual indifference. The patient may manifest symptoms of an intracranial neoplasm or cyst, such as headaches, impairment of vision or encroachment of the visual fields.

It is of interest that the well proportioned midgets are usually hypophyseal dwarfs. Their effort to emulate normal adult society results in midget intermarriages and the so-called Lilliputian villages. Since they are

usually hypopituitary, there is the associated hypogonital picture so even when married these individuals rarely have offspring.

LABORATORY DATA. The laboratory data in pituitary dwarfism are those which are usually collected in hypopituitarism and are indicative of impairment of many endocrine functions.

The basal metabolic rate is commonly low. It varies as a rule from minus 15 to minus 35 per cent. The fasting blood sugar level may be reduced. The serum sodium is sometimes low. There is usually either a total absence of or a definite reduction in the urinary excretion of the neutral 17 ketosteroids and the pituitary gonadotropins. In the case of primary ovarian insufficiency there is no significant deviation from the normal average response to the administration of glucose or insulin. The urinary content of follicle stimulating hormone is greatly elevated as a rule and the 17 ketosteroid excretion is only slightly increased.

ROENTGENOGRAPHIC DATA. Roentgenograms of the skull of the hypophyseal dwarf disclose signs of adenohypophyseal somatotrophic insufficiency. The face is small in relation to the cranium, which thus remains largely infantile in variety. The brow retains the verticality of infancy. The diploic layer of the calvarium is hypoplastic. The frontal sinuses are poorly developed. The body of the sphenoid usually remains cancellous bone.

The sella turcica is infantile and the antra are poorly developed. The alveolar processes are hypoplastic and crowding of the teeth is pronounced. If deciduous teeth are retained when the permanent set appear.

There is delay in the appearance of the epiphyseal centers. Closure of the epiphyses in all the bones is delayed. Permanent non-union of the epiphyseal centers to the shafts of the long bones may persist.

The skeletal system and viscera are small and delicate but essentially well proportioned.

Differential Diagnosis. Primary hypopi-



FIG 164 Werner's syndrome (Figs. 164 to 170 from Pomeranz M M Radiology 51 521-524 1948 abstr in 1949 Yearbook of Orthopedics and Traumatic Surgery pp 443-446 Chicago Year Book, 1950) White female 35 years old. The patient shows premature aging with a "birdlike" facies.



FIG 165 Werner's syndrome (Same patient as Fig. 164) Foot and lower leg showing lateral malleolar ulcer. Trophic ulcers are typical findings in Werner's syndrome and this one caused the patient to seek medical care.

tuitarism must be differentiated from other causes of dwarfism. These include

1 **SECONDARY HYPOPITUITARISM** This condition will result from anything producing secondary atrophic changes in the anterior hypophysis such as

A. *Malnutrition* This may result from conditions such as the celiac syndrome which includes idiopathic steatorrhea, cystic fibrosis of the pancreas and nontropical sprue.

B. *Congenital or Acquired Cardiac Diseases* These appear to produce their effects on the basis of anoxia and inanition.

C. *Renal Disease* This of course refers primarily to renal dwarfism of rachitic type (Figs. 223 to 227). This can result from disease involving either glomerular or tubular portions or both. The azotemic effect here may produce secondary hypopituitarism.

The high phosphorus retention of the glomerular variety versus the excess calcium loss in the tubular type has been discussed under kidney dysfunctions related to bone. Secondary hyperparathyroidism is also a consideration here producing deformities.

2 **CRETINISM OR HYPOTHYROIDISM** It is possible that this may produce secondary hypopituitarism through lack of stimulation of the pituitary by thyroxine. However the more likely relationship is simply poor formation of the epiphyses and deficient growth of bone and all tissues in general because of thyroxine deficiency (Figs. 152 to 159).

3 **IDIOPATHIC PITUITARY DISTURBANCE REPRESENTED BY PROGERIA.** The term progeria means "prematurely old" and describes a form of infantilism associated paradoxically with premature and rapidly developing senility.⁶ This is not clearly a pituitary lesion. It is a rare disease found in children that is characterized by dwarfism and premature senility. The senility is evident by the appearance of pronounced cachexia. Arteriosclerotic changes are found throughout the body at a very early age. In the teens these individuals may suffer occlusion of coronary vessels, undergo myocardial infarctions and die of such diseases.

The clinical signs may be observed as early as 1 year of age and noted by failure to gain weight, very slow growth and loss of

hair and subcutaneous tissue. The epiphyses unite prematurely and the bones show osteoporosis.⁴

These patients show a striking similarity in appearance (Fig 164). Both sexes are almost completely bald. There are great loss of subcutaneous tissue, beaknose and chin retraction. The eyes appear extremely large and prominent. The skin over the whole body is very thin and atrophic and quite adherent seemingly because of the lack of subcutaneous tissue. The chest is narrow, the abdomen protuberant. The skin is blotchy and yellowish brown. The joints of the extremities are prominent since there is so little muscle mass they are prominent relatively but they also appear to be thickened and stiffer than usual. It is quite probable that this is due to the severe development of premature hypertrophic osteoarthrits.

In corroboration of this we note also that

these markings show quite prominent joints of fingers and toes. Vessel markings are very prominent again because of the thin skin and the atrophy of subcutaneous tissue. The genitalia do not appear to be abnormal for the particular age of the patient. Trophic ulcers are seen in the feet and the legs (Fig 165).

X-ray Studies These cases of progeria show normal sella turcica and early union of the epiphyses of the extremities. Osteoporosis is common. There are peripheral vascular calcification and metastatic soft tissue calcification (Figs 166 to 170).

Laboratory Studies These are normal for basal metabolic rate, serum sodium, potassium and chlorides. Laboratory studies show no specific diagnostic factors as far as the authors can ascertain except that which may be expected in an aged individual. This condition may be regarded as a markedly accelerated process of normal



FIG 166 Werner's syndrome (Same patient as Fig 164). Foot and ankle. Anteroposterior and lateral views showing pronounced osteoporosis and calcification of the blood vessels.



FIG. 167 Werner's syndrome. (Same patient as Fig. 164.) Both feet Anteroposterior view. Note advanced osteoporosis. The right foot is deformed as a result of poliomyelitis at 9 months of age. Vessel calcification as well as meta static calcification is observed.



FIG. 168 Werner's syndrome. (Same patient as Fig. 164.) Elbow Lateral view showing generalized osteoporosis with pathologic calcification in the triceps tendon area.

aging with a very poor prognosis. An individual may complete his whole cycle of life well before the middle teens.

4 OVARIAN AGENESIS OR HYPOFUNCTION (TURNER'S SYNDROME?) These cases show the definite chemical finding of high urinary gonadotropic titers and this can easily be compared with the absence of gonadotropins in true hypopituitarism. Furthermore, these cases are characterized by the following findings: complete lack of breast development; small or only moderate amounts of axillary or pubic hair; short stature; webbing of the neck; cubitus valgus; late union of epiphyses; osteoporosis; decrease of 17 ketosteroids; and even coarctation of the aorta.

5 PRIMORDIAL DWARFISM OR PYGMYISM Primordial dwarfs, or pygmies, are com-

pletely normal people from the endocrinologic point of view. This is merely a familial phenomenon and on a purely hereditary basis, as for example the pygmy tribes of central Africa. These people, who are of good intelligence, are born abnormally small. Growth continues in a slow manner. They mature sexually at the proper time and their epiphyses unite at a normal time.

Chemical studies in these patients are entirely normal. They are capable of normal reproduction, usually transmitting the dwarfism to their children. In-breeding will perpetuate the condition and conversely it may be bred out as well.

6 ACHONDROPLASIA In which there is dwarfism of the extremities in particular. Achondroplastic dwarfs present disproportion in relation to the trunk and the head.



FIG 169 Werner's syndrome. (Same patient as Fig 164) Hand Anteroposterior view. Observe the severe calcification and the vascular sclerosis.



FIG 170 Werner's syndrome. (Same patient as Fig. 164) Lumbar spine Lateral view showing mild osteoporosis of the vertebral bodies with the presence of good subchondral bone. The abdominal aorta is calcified. Limb osteoporosis is much more severe in this instance than the spine changes.

These are relatively normal in relation to the upper and the lower extremities which are the dwarfed portions (Figs 73 to 76). The process occurs because of abnormality of the epiphyseal plates and cartilages especially in the long bones. (See Achondroplasia, page 131.)

7 OSTEOGENESIS IMPERFECTA (see Osteogenesis Imperfecta page 91 and Figs. 17 to 28)

Treatment. To this date specific and effective treatment of this condition is not available. It is true that growth principle from the anterior pituitary would be rea-

sonably effective if it were available in an effective preparation. It is true that such growth hormone is available for use in animals but to the knowledge of the authors an effective type for humans has not yet been obtained. When as and if this occurs it would be quite effective in these cases if instituted early enough. Obviously after the epiphyseal plates have fused it could not be effective. The use of gonadotropins, thyroid extract, testosterone and a high protein, high calcium, high phosphorus diet with ample vitamins is not unreasonable.

Estrogens also of course would be desirable in the female. Surgical excision of the pituitary adenoma tumor or the craniopharyngioma have been reported but favorable effect upon growth has usually not resulted since pituitary destruction has proceeded too far. Surgical excision of the lesion may be of value in reducing ocular manifestations.

Prognosis. This is good unless the tumor involved is of a malignant type. Generally these tumors that do cause destruction of the anterior pituitary are benign in type and do not affect longevity. These patients therefore will live out a normal span of life with no particular problem.

ACROMEGALY (PITUITARY)

(Syn. *Marie's malady*, *pachyacria*, *megalacria*, *dystrophia autogenetica*.)

Definition. Acromegaly is a chronic disorder occurring after epiphyseal closure and skeletal maturation are completed. It results from reinvigoration of growth of the bony skeleton. It is due to excessive productivity of the anterior portion of the hypophysis.

Historical Notes. The first authentic description was given by Saucerotte and Noël.¹ In 1886 Pierre Marie² published his well known paper and gave the name acromegaly to the disease from *akron* (end) and *mega* (large). He described 2 cases and quoted 5 from the literature with similar features and believed that the cause was hypofunction or dysfunction of the pituitary gland.

Von Recklinghausen suggested the name *pachyacrie* because thickness of the extremities is a constant feature. Fritsche and Klebs³ demonstrated the role of the hypophysis in producing acromegaly. The following year O. Minkowski⁴ ascribed the syndrome to hypophyseal disease.

In 1888 Marie published a book in English and drew particular attention to the enlargement of the hypophysis and the expansion of the sella turcica and also to the presence of gigantism with acromegaly.

Oppenheimer⁵ was the first to recognize

enlargement of the sella turcica during life by means of roentgenograms. Benda⁶ showed definitely that the pituitary lesion associated with acromegaly was an adenoma consisting of cells containing eosinophilic granules, that these granule-bearing cells were similar to those which are present in large numbers during the growth period in normal persons and that acromegaly was in all probability a result of overactivity of the pituitary gland.

In 1909 Gramegna reported the first example of a pituitary tumor treated by roentgen rays. He obtained gratifying results. Cushing⁷ demonstrated experimentally in the same year that pituitary extirpation retarded skeletal development and thus came to the conclusion that acromegaly and the related condition gigantism were attributable to hypertrophy of the gland.

In 1921 H. M. Evans⁸ was able to produce gigantism in rats by repeated injections of extracts from the anterior lobes of beef pituitaries. Putnam in 1928 experimentally produced acromegaly in dogs by similar methods.

Incidence. Acromegaly is a rare disease. It occurs in all parts of the world and in all races; the incidence among Jews and Swedes being relatively high. Males and females are affected in equal numbers.

Obviously all cases of gigantism have characteristics of acromegaly. Therefore one can understand Fairbank⁹ and other authors who describe cases as childhood and adolescent acromegaly. The authors of the present volume prefer to classify cases as acromegaly when these cases develop in individuals who have reached complete skeletal maturation under normal conditions. Then when a pituitary hypersecretion occurs, growth reactivation with typical changes occurs. The earlier in life the pituitary hyperfunction occurs, the closer the case will be to gigantism.¹⁰ The later pituitary hyperfunction occurs, the more it will be acromegalic.¹¹

Sometimes a general infection appears to be a precursor, for example, of measles and typhoid fever.

In a series of 2 023 intracranial tumors Cushing⁷ found 360 (17·8 per cent) to be hypophyseal adenomas. Of these 360 adenomas, one fifth were chromophile.

Etiology. The cause of the development of eosinophile hyperplasia or adenoma is unknown. There is a hereditary factor. Some cases have been observed to be familial. It is well to keep in mind the following facts relative to the growth hormone. They are as follows:

1. Although clinical and experimental evidence has previously indicated that skeletal growth depends upon the pituitary gland, it was not until 1921 that Evans and Long demonstrated that a saline emulsion made from the anterior pituitary lobe of fresh glands of cattle contained a growth hormone. This emulsion when injected daily ($\frac{1}{2}$ to 1 cc.) intraperitoneally into young rats, accelerated their skeletal growth rate compared with control animals and continued this growth for 200 days or more after that period in the life of an untreated rat when growth normally stops—i.e., about the one hundred fiftieth day of life.



FIG 171 Acromegaly Skull. Lateral view. Note the prognathic overgrown mandible, the enlarged sella turcica, the large frontal sinuses and the thickening of the calvaria.

FIG 172 (Bottom) Acromegaly. Both hands. Anteroposterior view. Observe the secondary bony overgrowth of the phalanges and the metacarpals. The ulna and the distal phalanges are particularly hypertrophied.

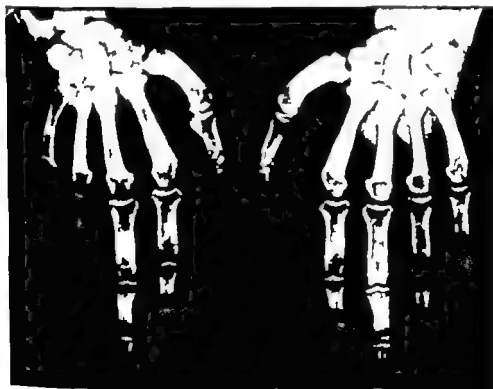




FIG 173 Acromegaly (Figs. 173, 174 from Dr Eugene P Pendergrass) White male 36 years old Skull Lateral view An excellent example of overgrowth of the supraorbital ridge. The sella turcica is considerably enlarged The mandible also is overgrown.

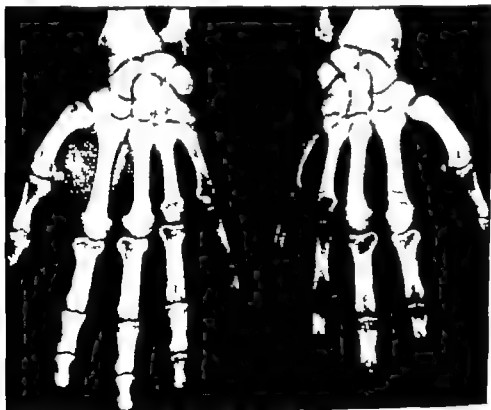


FIG 174 Acromegaly (Same patient as Fig 173) Both hands. Anteroposterior view Note the spadelike configuration with the large size of all the bones. There is some overgrowth of the distal phalangeal tufts.

Evans termed his normal rats injected with pituitary emulsions hypophysis giants" and stated that "they were twice as heavy as the largest ones known to us from our own and published records for this animal species."

2 The increase in body growth of rats produced by the hormone is attributable to a direct action on the tissues and is independent of any increased secretion by other endocrine glands.

3 The muscles and the viscera grow as rapidly as the skeleton and the body as a whole.

4 After hypophysectomy in rats it has been postulated that a "calcium barrier" or "closing membrane" appears which ends normal activity at the epiphyseal lines. The growth consequently ends. When growth hormone is injected into hypophysectomized rats, the closing membrane disappears. Cartilage cells at the epiphyseal line begin to proliferate and differentiate again into bone. Bone growth will resume. Thus it can be said that rats will maintain an arrested epiphyseal line. This is in contrast with the true obliteration of the epiphyseal line in the human. A rat therefore develops gigantism, not true acromegaly on the experimental injection of growth hormone.

5 Membrane bones (for example those of the cranium) are unaffected by hypophysectomy. Osseous tissue that has already been laid down also undergoes no change.

The experiments on animals are interesting, particularly since an active growth hormone works in them. Conclusions from animal work cannot be fully applied to humans. Infundibular in animals for instance may be increased by pituitary hormone. This conclusion is not necessarily true in the human.

The anterior hypophysis and the thyroid are the glands most closely related to osteogenesis because suppression of one or the other suspends growth and consequently skeletal development. The first because of its growth effects, intervenes in osteogenesis by acceleration of the proliferation in the cartilage of the epiphyseal disk an effect

which appears to be the principal one and for which reason it has been mentioned as "chondrotrophic factor." It also stimulates the normal processes of osteogenesis in diaphyso-epiphyseal union.

It is obvious that growth presupposes nitrogen retention for the synthesis of the new proteins and it is known that the anterior hypophysis stimulates growth not only of the skeleton but also of all tissues.

Skeletal hypertrophy is manifest in endochondral and periosteal new bone formation.

In a pronounced condition there is enormous subperiosteal thickening on the front and the sides of the vertebral bodies so that they become much wider horizontally than thick vertically. This change is most pronounced in the lower thoracic area.

Characteristic endochondral bone formation however is seen at the costochondral junctions where an irregular cartilaginous hyperplasia causes the acromegalic 'rosary' and with advancing ossification produces lengthening of the ribs and a consequent expanded chest.

Reiss Fernandes and Golla¹¹ found that the administration of 50 mg daily of testosterone propionate causes regression of the cartilaginous overgrowth of ribs in an acromegalic patient within 10 days.

Every bone may show great vascularity especially those of the cranial vault and least of all the mandible. Every bone may be abnormal in shape and appearance and all the bones concerned in the formation of a joint may show signs of rheumatoid arthritis. Very rough muscular tuberosities are common.

Clinical Characteristics. In general signs and symptoms are (1) those which are brought about by disturbance of the internal secretory mechanism of the hypophysis and (2) those caused by pressure of a tumor upon surrounding cerebral structures. The initial symptom is often headache between the temples.

Dullness becomes progressive to somnolence and lassitude. Fatigue and depression are frequent accompaniments.

The face becomes coarsened owing to a thickening of the nose and the lips

The skin becomes darker and thicker developing folds, and an increasing amount of hair appears.

The hands and the feet gradually increase in size. This enlargement first is of the soft parts but later the width is increased owing to osseous hypertrophy. There is great widening of terminal phalanges producing the characteristic spadelike hand.

Other changes noted are the early appearance of amenorrhea. In men increased sex potency is followed gradually by declining sexual power.

Specific changes by system are as follows:

1 *The Skull* The skull may be higher on one side than the other. It is considerably thickened. The ridges are extremely prominent and the external occipital protuberance enlarged. The cranial sutures may be obliterated. The changes in the facial bones are characteristic. There are thickening and enlargement of the zygomatic arches and of the malar bones, and especially of the lower jaw which becomes prognathic owing to overgrowth and also to changes in the temporomandibular joint.

The teeth are spaced and wide apart because of the increased jaw width.

The foramen magnum is preternaturally anterior because of atrophy of the basilar process of the occipital bone.

The occipital condyles are reduced in size and their axes altered. The head is consequently carried in a more extended position. The condyles also press upward into the skull.

Apposition of bone may occur from the nasal spine to the alveolar process with a relatively small ethmoid. The temporal fossae are very deep.

2 *The Lower Jaw* The hypertrophy of the lower jaw with that of the bones of the upper jaw and the face increases the length of the face and gives the characteristic oval face of the acromegalic person.

3 *The Vertebral Column* This commonly shows a pronounced cervicodorsal kyphosis

with a compensatory lumbar lordosis. Scoliosis is also frequently present. The anterior surfaces of the vertebrae are greatly roughened and exostoses may be seen. In some examples the bodies are ankylosed and the disks absorbed. The transverse processes of the vertebrae are frequently enlarged and the accessory processes enormous. The intervertebral foramina are narrowed and the vascular foramina enlarged. There is atrophy as well as hypertrophy and this gives rise to the kyphosis.

4 *The Clavicles* The clavicles are rough and thickened. Both ends are very thick and pitted.

5 *The Thorax* The anteroposterior diameter is greatly increased and the sternum may protrude as well as the ensiform cartilage hence the "double bossae."

6 *The Ribs* The anterior ends of the ribs are very broad. The subcostal groove is deep. Irregular flanges of bone may be present on some of the ribs which are much thickened at the sites of muscular attachment and greatly roughened. The cartilages of the ribs may be ossified.

7 *The Scapulae* The bones are broad and rough and strong processes of bone may project from the ventral aspect of the superomedial and the inferior angles. The spine, the acromion and the coracoid processes are rough and greatly increased in size.

8 *The Humerus* The humerus is much thickened and rough. The tuberosities and the condyles are much enlarged. The deltoid impression is particularly well marked.

9 *The Radius and the Ulna* These are enlarged. They are often deeply excavated.

10 *The Hand* The articular surfaces of the hands are extremely expanded and strong. The shafts of the metacarpals and the phalanges may be slender. The bones of the carpus are large and their processes strong. The separate bones tend to coalesce. Osteophytes may be found on the carpal bones, the metacarpals and the phalanges.

The more obvious changes occur in the hands and the feet especially in the carpal and the tarsal bones. The heads of the

phalanges may show outgrowths or tufting" on radiographic examination (Figs 172 and 174). The great and progressive increases in the size of the hands and the feet which is owing to the thickening of the soft tissue as well as to skeletal changes results in the characteristic need for an outsize in shoes and gloves. The fingers are thickened somewhat square in their termination giving the appearance of a spadelike hand. The long bones of the upper and the lower limbs may show considerable periosteal thickening and deformity or may appear normal.

11 The Pelvis. The pelvis is very broad and the sacrum wide. The crest of the ilium is thick and rough, as well as the attachments of the muscles.

12 The Sacrum. The sacrum may be rotated with the longitudinal axis horizontal. The spine of the axis is large and thick and the articular processes and surfaces of increased size.

13 The Femur. The femur often shows a third trochanter and the condyles are much increased in size and roughened. The attachments of the muscles are much increased.

14 The Patella. The patella is thick and very rough and may show osteophytes.

15 The Tibia and the Fibula. These are frequently ossified together and both bones are rugged, deeply excavated and crested. The tarsi are much thickened and the tuberosities (especially of the os calcis) much strengthened. Often flatfoot is present.

16 The Joints. Arthritis may follow changes at the articular surfaces of the bones and bony exostoses in the neighborhood of the joints may limit movement greatly. A part of the skeleton such as one big toe at times appears to be more susceptible to the growth hormone and may become enlarged quite out of proportion to the rest of the skeleton.

17 The Muscular System. Hypertrophy of the muscular system, associated with abnormal muscular strength, may occur in the early stages but early strength may be succeeded by muscular atrophy and atony.

18 The Soft Tissues. The tongue is

greatly enlarged and the papillae prominent. It may be unable to find room within the mouth and may interfere with articulation and tend to obstruct the air passages in the recumbent position. The lips become thickened, protuberant and negroid in appearance. These changes in the lips and also in the nose may occasionally precede the skeletal changes.

The skin and the subcutaneous tissue are thick, the pores enlarged and sebaceous and sudoriferous glands hypertrophied. Fibromata mollusca may be seen. Excessive sweating on the whole body may be troublesome and intractable together with the greasiness of the skin resulting in persistent malodor.

The hair on the trunk in both sexes may become abundant and coarse, the thick greasy hairy skin contrasting with the fine dry hair free (or covered with delicate hair) skin of the hypopituitary state.

19 The Respiratory System. In both sexes the voice becomes deep and resonant, owing to the enlargement of the larynx and the increased width and resonance of the air sinuses though the mucous membrane may be so thickened that respiratory obstruction may on rare occasions require tracheotomy. The lungs are enlarged proportionately with the thorax.

20 Cardiovascular Changes. The heart may be enormously hypertrophied and also all the coats of the peripheral blood vessels. Hypertension is followed by hypotension in the later stages. Acrocyanosis and Raynaud's phenomena sometimes occur in acromegaly. Varicose veins are not uncommon and superficial phlebitis or hemorrhoids may be superimposed.

21 The Nervous System. The sense of smell may be impaired owing to hypertrophy of the nasal turbinal bones. Pressure on the optic chiasm leads to optic atrophy, bitemporal hemianopsia and later to complete blindness of one or both eyes. Ocular palsies may result from pressure on the third, the fourth or the sixth nerves. Involvement of the fifth nerve may cause pain and

hyperesthesia over one or more of its divisions

Deafness may be due to involvement of the auditory nerve or the middle ear

Headache may be very severe and bursting in character. It is occasionally migrainous and associated with vomiting. The severe headaches are often intractable.

Paresthesias of the hands and the legs may be early symptoms. But true neuritis follows when somatic nerves are caught in obliterated intervertebral foramina.

Areas of sclerosis may arise in the spinal cord with resulting ataxia and pseudotabes. True acromegaly may also be associated with syringomyelia.

Speech may be sluggish and slow memory often being impaired and the general behavior characterized by apathy and lack of initiative. Depression, irritability, negativism, melancholia, mania and delusional insanity may be additional symptoms. (In the early stages or in relatively mild examples however there may be great alertness, energy and drive.)

The cerebrospinal pressure may be great, headaches being relieved temporarily by withdrawing some 30 cc. of cerebrospinal fluid.

22 The Sexual System. An initial increase in libido may occur rarely in both sexes. More commonly amenorrhea and impotence are early features and almost invariably are present in the later stages. Nevertheless interference with sex function may not be obvious for 10 or more years though skeletal and other manifestations are progressive. Normal menstruation, pregnancy and parturition occasionally take place when the acromegalic process is well advanced. In acromegalics also impotence and amenorrhea are often associated with atrophy of the genitals.

In both sexes there may be an extensive growth of coarse oily hair over the trunk. In the female abnormal hairiness sometimes develops on the face and the extremities and the hair of the head falls out as in primary adrenal virilism.

Adrenal cortex hyperfunction may be a factor in acromegalic diabetes.

In the later phases of acromegaly adrenal cortex hyperfunction may be followed by hypofunction.

THYROID DYSFUNCTION. Although the basal metabolic rate is increased in about 50 per cent of acromegalic persons, a clinical picture of thyrotoxicosis is found only in approximately 5 per cent. In these, as well as in other examples of acromegaly, histologic section shows a colloid goiter.

A. C. Davis¹² studied 271 cases at the Mayo Clinic and came to the conclusion that thyroidectomy in the presence of acromegaly is always associated with a high surgical risk.

LABORATORY DATA. Some 20 per cent of patients affected by acromegaly have glycosuria and elevated blood sugar. In about half of these the carbohydrate tolerance curves are indistinguishable from those discoverable in diabetes. A small percentage act as such; their tolerance progressively decreasing. Complications such as boils, cataract and gangrene appear. Even death in coma may result.

An adequate and normal response may often be obtained with the use of insulin. Most conditions run a benign course. The severity of the diabetes tends to parallel that of acromegaly, diminishing or disappearing in remissions. Removal of a pituitary eosinophile tumor may immediately abolish the diabetes, while incomplete removal may accelerate the response to insulin.

Hyperglycemia may be followed by hypoglycemia and increased tolerance if hyperpituitarism is followed by hypopituitarism. Polyuria and polyphagia may occur with or without diabetes.

Coggeshall and Root¹³ found that the average interval between the onset of acromegaly and that of diabetes was 9.2 years.

The basal metabolic rate is elevated early in the disease but commonly is subnormal in the late stages.

According to Cushing¹ the presence of

prolan in the urine is noted in active acromegaly and has been found to furnish an index of the activity of the chromophile adenoma.¹¹ The calcium excretion usually is elevated but is largely dependent upon the amount of calcium intake.

The excretion of creatine and creatinine in the urine is greatly increased in acromegaly during the active phase and apparently is due to the anterior pituitary hyperfunction.

ROENTGENOGRAPHIC DATA. The early stages are not recognizable roentgenographically. It is necessary that the process shall have progressed to macroscopic dimensions to be discoverable. It must be kept in mind that the roentgen signs are based upon the disappearance of osseous or of calcific substance or of new bone formation and deposition of calcified material.

The bones of the skull as we have seen are especially distorted by the growth process.

The frontal sinuses become large and projecting. The calvarium is heavy. The base of the skull shows less thickening but the mandible becomes large and widened with, as aforesaid, spacing of the teeth and an increasing prognathism of the lower jaw (Figs. 171 and 173).

The changes in the sella turcica are the most important. It may be enlarged along with the remainder of the skull.

Roentgenographic changes of the bone in and about the sella depend for the most part on the direction in which the expanding tumor exerts its pressure.

When an adenoma develops the measurements of the sella turcica increase beyond the 10 to 12 mm. normal anteroposterior distance. The floor may be eroded with excavation beneath the anterior clinoids. The posterior clinoids may also be eroded and pushed backward and sometimes destroyed.

There is a broadening of the phalanges and hooding and tufting of the terminal ones. This is pathognomonic (Figs. 172 and 174).

Hyperostosis of bones along the vertebrae

is likewise a frequent sign. It is productive of a rigid kyphosis and the characteristic posture of the disease. Overgrowth of the vertebral bodies, rings of bone that form complete margins added to the original vertebra body is observed.

Pronounced arthritic changes are noted in the joints and exostoses are found in many places in the advanced stage of the disease.

A diffuse generalized skeletal sclerosis which includes the skull complicates these primary changes so that there is massive thickening of the cranium and other parts of the skeleton.

Osteophytes may extend into tendons and ligaments.

Pathology. The pathology of acromegaly was described by Fritzsche and Klebs² several years before Marie.³ The essential feature is the continued oversecretion of growth hormone producing skeletal and visceral changes comparable with those of experimental acromegaly. The pathology is related to an increased activity and hyperfunction of the eosinophile (chromophile) cells of the pituitary gland. These usually multiply and form an adenoma of a benign variety. The end result is hypertrophy of the gland and pressure upon the surrounding sella turcica and usually upon such nearby brain structures as the optic chiasm.

The changes in the other endocrine glands are multifarious. For example there may be increased and later decreased production of adrenocorticotrophic hormone by the eosinophile cells. There may be failure of secretion of other tropic hormones for example gonadotropic, and there may be encroachment of the eosinophilic cells upon the basophilic cells. The pathologic changes depend to some degree upon the phase of the disease. Overactivity may be followed by exhaustion of pituitary cells and under activity.

The cortex of both adrenals is usually hyperplastic and multiple adenomas frequently are present. The thyroid is enlarged in some 50 per cent of patients, change usually being an increase in vesicular colloid

The parathyroids may be enlarged and adenomas therein have been recorded. Enlargement of the thymus and diffuse lymphoid hyperplasia which also occurs both with Addison's disease and with adrenal cortical adenoma or hyperplasia are common.

The pancreas may be normal or atrophic or may show hyperplasia with perhaps adenomas of the islets of Langerhans. This is attributable to the fact that in some species pituitary diabetogenic hormone produces hyperplasia of the islets before they degenerate.

The ovaries and the testes are usually atrophic. There is not much evidence relating to the histologic changes in the ovaries, although amenorrhea is common but they may be cystic and degenerated, free from follicles but rich in corpora atretica, small and fibrous or multilocularly cystic. The testes are often soft and flabby the seminal vesicles disorganized and the interstitial cells degenerated. Impotence is common in late stages of this disease.

The heart, the lungs, the liver, the spleen and the kidneys are greatly enlarged; the stomach is often double its normal capacity and both the small and the large intestine are increased considerably in length and in circumference.

There is massiveness of all bones of the skeleton the long bones being considerably thickened and the bodies of the vertebra enormously enlarged. Extreme thickening of the bones of the skull is an almost constant feature (Figs 171 and 173).

Diagnosis. The diagnosis as a rule is made easily. It is based on progressive changes in the skull, the face and the extremities and on the roentgenographic features and laboratory data. There are (1) large extremities (2) awkward movements (3) thickening facial features (4) drooping of the shoulders with the hands falling near the knees in advanced examples giving the appearance of simian man.

Differential Diagnosis. The early stages of acromegaly frequently may be confused with rheumatoid arthritis or pulmonary

osteoarthritis. The late stage of the disease offers no problem.

Complications. Some of the complications of acromegaly are (1) increased intracranial pressure (2) diabetes mellitus (3) hyperthyroidism (4) arteriosclerosis, (5) hypotension (6) myocarditis (7) asthenia, (8) blindness and (9) osteoporosis.

Treatment. The objectives of treatment are (1) relief of pressure from an expanding tumor both on the pituitary tissue itself and on surrounding structures and (2) relief of hyperhormonal effects.

Early diagnosis is essential if treatment is to be adequate. It is advisable to carry out roentgen therapy or exploration as early as possible.

Schuetter, Bailey and Vaughan¹⁴ found that the sinusoidal variety of adenoma (e.g. where the relations between cells and vascular supply of the normal anterior part of the gland is unaffected) were as a rule, more radiosensitive than the diffuse kind.

The eosinophilic pituitary adenomas take origin from the anterior lobe of the hypophysis. As they grow they compress and destroy the residual normal tissue. They distend the dural casement which lines the sella. This envelope may rupture, permitting the extrusion of the tumor into the intracranial cavity. Here it may compress the hypothalamus and also extend laterally into the temporal lobe. The tumor erodes the sella walls producing the characteristic "ballooned sella" which may be seen in the roentgenogram. As the tumor grows, it distends its dural capsule upward and compresses the optic chiasm producing one of its most characteristic manifestations—namely failing vision and bitemporal hemianopsia.

Successful therapy may result in regression of soft tissue lesions, improvement in visual-field defects, decrease in size of the sella turcica, relief of headaches and reestablishment of menstruation.

Where there is involvement of cranial nerves especially of the optic nerve surgical removal of the pituitary tumor is indi-

cated Improvement takes place in about 75 per cent of patients.

Röntgen treatment of the pituitary is often curative.

Some clinicians (Goldberg and Isser¹²) believe that beneficial results are obtainable from the administration of estrogens and androgens. They are considered to inhibit increased pituitary function. Large doses have to be administered over a prolonged period.

Studies on the output of creatine and creatinine in acromegalic persons have furnished convincing evidence of the inhibitory effect of large doses of estrogen and androgen on the anterior pituitary lobes.

Prognosis. Acromegaly is usually a chronic progressive disease. The changes may be sufficiently slow to last a lifetime without grave disability, however many are completely incapacitated within a few years. Periods of remission and exacerbation take place in the protracted varieties. A non-progressive phase may last many years. The more active the disease obviously the worse the prognosis.

OSTEOPOROSIS ASSOCIATED WITH ACROMEGALY (PITUITARY)

A negative balance of calcium represents a very interesting finding associated with acromegaly.¹ This was established by determining excess excretion of calcium in the urine but not in the feces. There was also found a concomitant negative balance of nitrogen. Correlation between hypercalcuria and negative nitrogen balance was clearly indicated by study of one case in which there was the greatest negative nitrogen balance. In this case there was also the greatest amount of calcium excreted in the urine. In another case in which there was a positive nitrogen balance there was no excess calcium excreted in the urine.

Albright² reported upon two cases of this disorder. These cases were placed upon high nitrogen intakes. Despite this regimen which produced a positive balance of pro-

tein they still maintained negative calcium balances. However when estrogen was administered the calcium loss was reduced. This would indicate that estrogen stimulus is greater upon bone formation than upon nitrogen retention. Albright found in these studies that the serum calcium and phosphatase values were within normal limits the serum phosphorus levels were on the high side of normal. These findings are typical of postmenopausal osteoporosis.

Many explanations for the osteoporosis associated with acromegaly have been advanced. Possibly the most reasonable one is the fact that the osteoporosis can be related to hypogonadism which, of course occurs commonly in most cases of advanced acromegaly. Under these circumstances the condition would be simply a postmenopausal osteoporotic condition.

Such an explanation was dramatically borne out by metabolic studies done by Albright² on two cases to study the effects of estrogens. In each case the negative calcium balance became a positive calcium balance and the serum-phosphorus level was lowered. In one case the serum phosphatase level became elevated. This could be interpreted as a stimulating effect upon osteoid and an excessive amount of osteoid tissue formation.

Of course certain fine points not clearly understood as yet might occur in these conditions for Albright's² case 18 which had normal follicle-stimulating hormone excretion and normal findings on testicular biopsy had a markedly negative calcium balance. Furthermore estrogens made this strongly positive. Certain interesting theoretical questions on bone-matrix formation are raised by these studies. The relative importance of estrogens and androgens is not yet clear. In any event the argument of hypogonadal effect in acromegaly is a good one.

The treatment therefore ought to be administration of androgens, estrogens, proteins, vitamins and minerals, as listed under postmenopausal osteoporosis.

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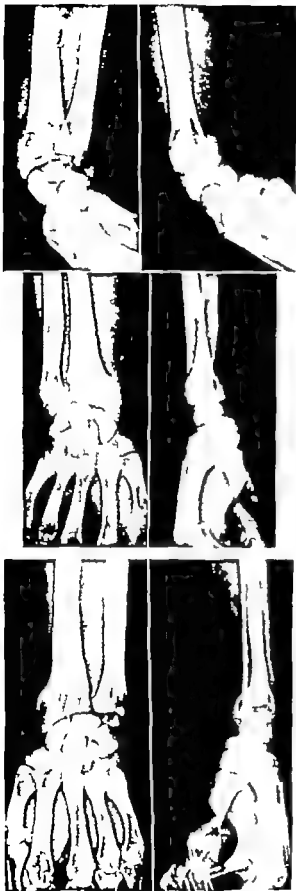


FIG. 176. Osteoporosis of disuse. White female 50 years old. A fall on the outstretched hand resulted in a comminuted fracture of the distal end of the radius and fracture of the styloid process of the ulna. (Top) Right wrist. Anteroposterior and lateral views (July 22 1949). Roentgenogram several days after injury shows the early zone of absorption in the distal radius at the fracture site. (Center) Right wrist. Anteroposterior and lateral views (August 22 1949 after one month in plaster). Roentgenogram taken in process of change of plaster shows advanced spotty osteoporosis of carpal bones. There is also osteoporosis of the metacarpal bones. The radius distal to the fracture site and the distal ulna are so osteoporotic that only thin shells of cortical bone are seen. These changes occurred despite the fact that the patient had actively used her right hand in plaster. (Bottom) Osteoporosis of disuse. Plaster immobilization was continued for a total of 8 weeks. Then intensive physical therapy and active function were instituted. Right wrist. Anteroposterior and lateral views (January 11 1950). The fractured radius is fully healed the ulna styloid tip is ununited. Marked improvement of bone structure and detail with repair of the osteoporosis have occurred.

Treatment. The therapeutic program should include

- 1 Minimizing complete bed rest to as short a time as possible
- 2 Maintaining muscle contractions and, where possible joint motion during fixation of a limb in plaster or traction
- 3 Resumption of active function without splintage as soon as bone and soft tissue healing permits.
- 4 Judicious use of physical therapy including active movement during and upon the discontinuance of local immobilization of a part.
- 5 The anabolic effect of testosterone can be used to conserve protein in cases of complete bed rest. If not contraindicated by systemic disease 25 mg 2 to 3 times weekly may be used.

6. The rebuilding of matrix and its recalcification by the use of large amounts of estrogen testosterone high protein and high calcium phosphorus intakes with vitamin D must await the ambulation of the patient. During complete bed rest the dangers of hypercalcemia with nephrolithiasis and nephrocalcinosis contraindicate the intensive hormonal and dietary treatment of osteoporosis.

POST TRAUMATIC PAINFUL OSTEOPOROSIS

(See Reflex sympathetic dystrophy, Sudeck's atrophy, acute bone atrophy, peripheral trophoneurosis, causalgia, reflex sympathetic dystrophy, mottled atrophy, traumatic osteoporosis.)

Definition. This is a condition characterized by decalcification of bone pain and

sometimes sympathetic phenomena such as color and temperature changes in the skin of the affected extremity (Figs 177-178). It is a rapidly progressive osteoporosis usually evident in the bones distal to the injured area.

Historical Notes. Causalgias following nerve injuries were described by Weir Mitchell.¹

Schliff² and Rasumovsky³ made extensive researches into the problem of bone atrophy.

Sudeck⁴ believed that the condition was acute bone atrophy associated with inflammatory joint lesions and observed the presence of this osteoporosis in the x-ray picture.

In 1918 and in 1923 from a study of gunshot wounds Hüggenreiner⁵ came to the conclusion that the phenomena of acute bone atrophy were attributable to injury.

Leriche⁶ advocated sympathectomy for this condition and referred to it as post



FIG. 177 Post-traumatic painful osteoporosis (Sudeck's atrophy). White male 49 years old. Sudden onset of pain in the metatarsal area of the right foot following violent setting-up exercises. Progressively severe pain and swelling supervened for the next 3 months in the right forefoot with inability to stand or walk properly. There were diminished oscillometric readings and skin temperature on the right side. Anteroposterior and lateral views of both feet (December 1953). There is pronounced spotty atrophy of all the bones of the right foot as compared with the left side. The mottling principally involves the cancellous portions of the tarsus, the metatarsals and the phalanges. There is also some cortical thinning.

traumatic ascending neuralgia. He felt that a predisposition on the part of the patient was more significant than the initiating injury.

Incidence. Reflex sympathetic dystrophy most commonly follows old fractures, sprains, lacerations or gunshot injury to nerve trunks and blood vessels.

An odd characteristic about this variety of atrophy is that it may be extremely severe following a trivial injury, e.g. a sprain or a contusion and also that it may take place in limbs which have *not* been immobilized (Figs. 177-178).

The condition is not uncommon.

Etiology. Post-traumatic painful osteoporosis or reflex sympathetic dystrophy is a vasomotor and trophic syndrome induced by sympathetic reactions to an external injury.

Injuries to major nerves and arteries predispose an individual to this condition. A prolonged series of pain impulses sets up a vicious circle of reflexes spreading through

a pool of many neuron connections upward, downward and even across the spinal cord and reaching perhaps as high as the thalamus.

Clinical Features. Post-traumatic, persistent painful osteoporosis is characterized by incomplete loss of function of the affected part, varying degrees of vasomotor and trophic changes and spotty demineralization of the skeleton in the area of the trauma (Figs. 177-178).

Pain, the most consistent symptom, does not follow specific nerve pathways. In some examples of the condition pain even spreads to the opposite extremity (contralateral phenomenon).

Distinctive sympathetic changes appear. The most frequent is vasoconstriction which induces whiteness or blueness in the affected area. Some cases may present a picture of vasodilatation with redness of the extremity. This is the so-called erythromelalgia of Weir Mitchell.¹

Clinically, the picture is swelling of the

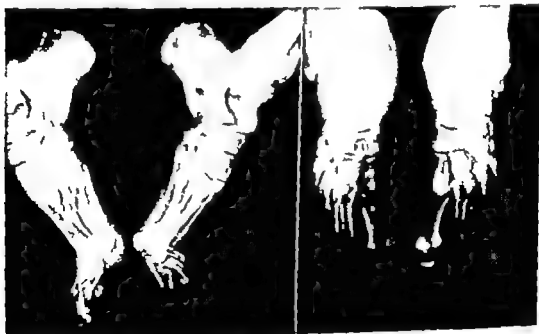


FIG. 178 Post-traumatic painful osteoporosis (Sudeck's atrophy). (Same patient as Fig. 177.) Treatment consisted of caudal sympathetic blocks repeated twice weekly for 3 weeks with excellent response. Proper metatarsal arch supports, physical therapy and encouragement of continued function with full weight bearing were used as adjuvant methods of therapy. The patient made a full clinical recovery. Anteroposterior and lateral views of both feet (June, 1954). The mottled zones in the cancellous bone have diminished in size and intensity. There is still residual cortical bone atrophy.

affected area with coldness, sweatiness and pallor or cyanosis. As the condition progresses the joints of the extremity become enlarged and stiff. The skin thins, becomes smooth and wrinkles disappear. The eventual appearance is severe skin atrophy, which also is observed in the intrinsic musculature. Fingernails and toenails develop ridges.[†]

The pain is deep, boring, diffuse and difficult for the patient to localize. It is sometimes described as "burning." One or more trigger areas are present, sometimes widely separated. A chief trigger zone is usually found near the original injury. Pressure on a trigger point usually causes a diffuse spread of the pain over a wide area, most characteristically up the limb.

ROENTGENOGRAPHIC FEATURES In the acute stage of the disease a cloudy and patchy appearance of the bone is seen. There are small nestlike rarefactions. When the process reaches a subacute or chronic stage there are many reduced, rarefied trabeculae with the appearance of generalized or mottled or spotty osteoporosis. The cortex is of diminished density (Figs 177-178).

The hands and the feet are the most common sites of involvement. The mottling especially affects the carpals and the tarsals and the heads of the metacarpals and the metatarsals. The porosity which occurs involves all the bones of the affected extremity, but the changes are greatest in the periarticular parts of the bones.

Pathology The pain and the sympathetic changes may be present without reflections in bone. Bone changes usually occur if the process lasts long enough.

There is porosity of bone of the affected part or parts. The degree of bone change is not related to the severity of the injury that initiates the process. It is considered to be the expression of a rapid remodeling of bone.

It has been postulated that there is a nutritional difference between the haversian systems and the interstitial lamellae. The haversian systems are better nourished than the interstitial lamellae; consequently in the former area there is a greater chance of

possible circulatory disturbances with resulting physicochemical changes than occurs in the latter. These changes are believed to be the cause of acute atrophy of bone.

It is felt therefore that a differential decalcification of bone is possible. The better nourished haversian systems are influenced (remodeled or decalcified) sooner and to a greater degree than the relatively ill nourished interstitial lamellae. It is obvious therefore that the latter by virtue of their higher calcific density will be differentiated from zones that have an ample blood supply, especially the zones of the haversian systems. The bone might be expected to show contiguous zones of differential calcific density. These zones however are of such minuteness that they cannot be projected separately on the relatively coarse-grained roentgen film.

The totality of these zones of varying calcific density together with the inability of the roentgenogram to reflect the changes separately may be a plausible explanation of the roentgenographic appearance of cloudiness and osteoporosis.

Diagnosis. The diagnosis is made on the basis of history of injury, even slight. It has been reported even after such a trivial insult as a hypodermic needle puncture.

Following the injury, severe intractable pain, sweatiness and trophic changes in the skin occur.

A therapeutic test^{*} is relief of symptoms even though it may be only temporary, following appropriate sympathetic block. In the upper extremity this would be a stellate block. In the lower caudal epidural or paravertebral sympathetic blocks are used.

Injection of a trigger point does not as a rule produce any effect, even a temporary one.

Differential Diagnosis. Sudeck's atrophy, repeatedly, has been mistaken for tuberculous loss of bone or any acute or subacute inflammatory process in the bone or surrounding soft tissues.

Treatment. Prevention is easier than cure. Injuries—even slight ones—when accompanied by pain that appears to be out of



FIG 179 (Left) Osteoporosis due to x ray irradiation. Colored female 53 years old. First seen in 1946 with complaint of pain in the left knee. Past history revealed that the patient had had heavy radium implantation and cross-fire irradiation for an adenocarcinoma of the cervix uteri. The total dosage was 4 626 r given through 4 anterior and posterior portals and 9,280 r given intravaginally. The original roentgenograms, which have disappeared, showed an undisplaced fissure fracture of the left femoral neck. A fibula bone graft was inserted in March, 1949 across the fracture into the femoral head with the hope that this would ensure healing of the fracture and blood supply to the femoral head. Anteroposterior view of left hip (May 1950). The fibular graft appears to be incorporated into the head and the neck of the femur. No fracture line is evident. The contour of the femoral head and neck appears good. The hip joint is normal. Osteoporosis is indicated by the prominent and sharply etched trabeculae of the entire proximal femur.

FIG 180 (Right) Osteoporosis due to x ray irradiation. (Same patient as Fig. 179 now 54 years old.) Now complains of pain in the left hip and lumps.

Left hip. Anteroposterior view (May 1951). The fibular graft is further incorporated. A large zone of aseptic necrosis is observed in the superior third of the femoral head. The hip joint is narrowed.

proportion to the injury, should be suspect. When this is accompanied by early signs of sympathetic hyperactivity, such as sweating, blanching or blueness, and coldness of the skin, such a case should be considered for vigorous active treatment.

Treatment should include local injections of procaine with early activity and use of the part. Proper splintage should not be neglected if indicated. Sympathetic blocks

may also be required and are effective early. Tetraethylammonium chloride may be used early for sympathetic effect also. It is a potent ganglionic blocking agent and its parasympatholytic side effects should not be overlooked. Cortisone and ACTH are also of value and have been reported upon* in the treatment of a form of reflex sympathetic dystrophy. Also, local use of hydrocortisone should be helpful.



FIG 181 Osteoporosis due to x-ray irradiation. (Same patient as Fig. 179 now 56 years old.) This is 18 months after the necrotic head was replaced with a Judet type acrylic prosthesis. Hip function is excellent. Patient walks painlessly without a cane. Anteroposterior and lateral views of left hip (November 1952). Note the shortening of the neck at the calcar femorale. This occurred because the brittle bone crumbled away during the insertion of the prosthesis. The position and the stability of the hip prosthesis is good.

An effective treatment consists of procaine blocking of the stellate ganglion if the condition is in the upper extremity or of lumbar sympathetic block if it is in the lower extremity. A "positive block" (one that relieves pain and produces dryness and increased warmth of the extremity) is of significance because it establishes the diagnosis of reflex sympathetic dystrophy. It may permanently relieve a mild condition and usually a severe condition. It may have to be repeated a number of times. If lasting effect does not occur even on frequent block. But if good temporary effect results from block surgical sympathectomy may be required.

If sympathectomy is done it appears that the preganglionic variety is the desired type. This is of particular importance in the upper extremity where removal of the stellate ganglion alone is unsatisfactory. If it is stellate removal alone the patient is more liable to epinephrine.¹⁴

OSTEOPOROSIS DUE TO X RAY IRRADIATION

X ray irradiation as well as that resulting from radioactive materials may affect bone. The result is a form of osteoporosis due not alone to disturbance of bone nutrition but also to direct damage to the osteoblasts.¹ The normal relationship between new bone formation and old bone absorption is thereby disturbed.

Osteoblasts are affected only temporarily by small doses of irradiation. Therefore bone change in the hip area for instance resulting in fracture may still heal (Figs 179 and 185). If the radiation has been too intense regeneration of osteoblasts and healing will not occur.

The reaction of bone to irradiation is summarized by Warren² as lowering of vitality that in some cases progresses to necrosis (Fig 180). The injury may be followed by excessive reabsorption or overgrowth of bone



FIG 182 Osteoporosis due to x ray irradiation. (Same patient as Fig 179 now 57 years old.) Patient's hip function still good. Anteroposterior view of left hip (April 1953). A 2 year follow up roentgenogram indicates progressive collapse of the calcar femorale with shift of the prosthesis toward a varus position. Several areas of the neck appear condensed and ragged, resembling sequestra.

as an attempt at repair. Normal balance of old bone absorption and new bone formation is disturbed.

Late changes are atrophy and condensation of bone. This sort of change reduces the normal bone vitality so that it becomes more susceptible to trauma and infection.

Specific effects upon osteocytes, osteoblasts and osteoclasts are still being investigated. Changes in chondroblasts have been studied carefully.² These cells have been shown to be markedly sensitive to radiation. It appears furthermore that adult bone is more sensitive to irradiation than either skin or mucous membranes.

It appears that the predominant clinical damage to bone following irradiation is osteoporosis.

In the past 20 years numbers of cases of pelvic carcinomas treated by irradiation (either radium implants or crossfire x-ray) have developed bone changes (Figs. 179 to 185). Four cases were reported in which femoral neck fracture occurred in one half to 1½ years following irradiation. Bone healing occurred in the four fractures after a long period of time. It is of interest that, several months before fracture occurred,³ two of these patients complained of moderate pain in areas subsequently fractured.

Twelve more cases of fracture of the femoral neck secondary to pelvic irradiation were reported⁴ in which the pathogenesis was considered to be vascular absorption and osteoclastic activity increase. Damage to the periosteum, the blood vessels and the bone cells was listed as a subordinate cause.

Biopsies⁴ made on three of 12 patients who had fractures showed thin fragile "shell like" qualities of bone. Microscopically the outstanding feature was osteoporosis. The trabeculae were very thin and bone cells were scarce.

These are reports of an interesting and not infrequent sequel to pelvic radiotherapy. There is a time lag of from 6 months to several years following the radiotherapy before pain and achiness begin in the hip or the knee.

X-ray studies after onset of symptoms will disclose an undisplaced or even displaced fracture of the involved femoral neck (Fig. 185).

The authors treated a case (A. D.) in which pain of this type and distribution occurred with the development of progressive limp over the course of a year. The major accent of complaint had been in the region of the knee. It was only after a year that hip roentgenograms were taken. By then these showed an undisplaced femoral neck fracture with still remarkably little pain and disability for such a fracture.



FIG. 183 Osteoporosis due to x ray irradiation. (Same patient as Fig 174 now 57 years old) Patient fell to the ground as she was walking. Examination disclosed external rotation and shortening of the left lower extremity with inability to bear weight or to raise the heel from the bed with the knee extended. Anteroposterior and lateral views of left hip (May 1953). There is a fracture of the prosthesis.

Figures 179 to 184 show the subsequent course.

The usual pattern in these postirradiation femoral neck fractures is a mild degree of pain in the hip and/or the knee which gradually and progressively increases in severity. Fracture usually appears first as a molecular fracture or fissuring of the bone. This progressively enlarges until separation and displacement have occurred (Fig 185). Healing is expected to be delayed due to the scarcity of bone-forming elements.

Furthermore on theoretical grounds aseptic necrosis would appear to be a common late complication (Fig 180).

ULTRASONICS

Historical Notes. Curie¹ discovered that, when subjected to pressure or tension, many crystals developed electric charges on definite crystal surfaces—the piezoelectric ef-

fect. Electrical energy can be converted into sound energy by means of crystals that show the piezoelectric phenomenon. Sound waves of very high frequency—far above the audible range—can be obtained in this way.

At present the most widely used method for producing ultrasonic vibrations is that which utilizes a piezoelectric crystal.

Ultrasonics as a science is only 35 years old but interest in it occurred considerably earlier. Galton² designed a kind of whistle that produced ultrasonic waves with a frequency of 25 000 cycles per second. König³ carried out a series of experiments with tuning forks only a few millimeters in length, which emitted ultrasonic vibrations. Perhaps the earliest investigator to set the upper limit of frequency for audible sound at its correct value of 20 000 c.p.s. was Schulze.⁴

An ultrasonic wave is entirely similar to



FIG 184 Osteoporosis due to x ray irradiation (Same patient as Fig 157 now 57 years old.) Arthroplasty of the left hip was performed in October 1953. The fragmented prosthesis was removed. The base of the neck was carefully remodeled. An F. R. Thompson vitalium prosthesis was inserted. The present result is one of excellent stability and function. Anteroposterior and lateral views of left hip. The F. R. Thompson prosthesis is in position.



FIG 185 Osteoporosis due to x ray irradiation. White female, 68 years old. Both hips. Anteroposterior view. There is marked osteoporosis involving the pelvis and the upper femora. The residual trabeculae are very prominent. Bilateral subcapital femoral fractures are present.

a sound wave except that its frequency is greater than 20 000 c.p.s. There is no fixed upper limit but, at the present time the highest ultrasonic frequencies obtained are about 1 000 000 c.p.s. The wavelengths at this extreme pitch approach those of visible light.

Sound is nothing but a wave motion in matter—usually air—of a purely mechanical variety. The term "sound" applies to any and all elastic waves in matter.

Tremendous forces are developed during the propagation of ultrasonic waves. Considerable heating may occur in any medium exposed to ultrasonic radiation depending upon the amount of energy absorbed. Chemical and biologic investigations utilizing supersonic waves require ultrasound of very high intensities. Tissues of different texture give different ultrasonograms. Tissues of abnormal texture can be detected by ultrasonography.

Ultrasonoscopy is the term used to indicate the application of ultrasonics to diagnosis—discovery of tumors for example. A narrow beam of very high frequency is directed at a given site in the body and the reflection of this beam by the various tissues is detected with appropriate ultrasound receivers. The character of the reflected beams depends on the nature of the tissues causing the reflection.

Fredrich Söllner and Rogowski¹² studied the effects of ultrasonics on bone marrow. They found that it could be strongly heated by ultrasonic radiation and that such energy could be transmitted across a joint.

All energy is dissipated in the form of heat and ultrasonic energy is no exception. When a medium absorbs ultrasonic energy, it becomes warm. Thus thermal effect of ultrasonics can be controlled and used advantageously.

Fredrich Söllner and Rogowski¹² suggested the use of ultrasonics in diathermy as long ago as 1932.

In the lower frequencies the whole body

is affected with high frequencies a particular small area may be involved as the ear with the higher frequencies there occurs a disruption of specific cells and the effect may even be specific for large molecules.

In reviewing the literature Bergmann¹⁶ has cited some 2 000 references to the physical aspects of ultrasonics.

Gregg⁷ outlined the physical and the biological action of ultrasonic vibrations as follows:

Vibration of this sort is characterized by extremely high pressures and large accelerations of the particles of liquid in the field. These in turn produce cavitation and if dissolved gas is present intense local agitation, high local temperatures and possibly electrical potentials. The net result is an exhibition of lethal and sterilizing effects, strong dispersive power, degassing processes, thermal and oxidizing effects, and coagulation.

Red blood corpuscles in physiologic saline solution can be destroyed by ultrasonic radiation. Some physicians in Europe have been using ultrasonics in therapy, e.g. in the treatment of certain neuralgias and malignant lesions. Use of this modality has begun to attain widespread use in this country also. Low energy outputs between 0.1 and 3 watts per square centimeter appear to be safe.

The first observations on the lethal effects of ultrasonics were made by Wood and Loomis who noted that fish, frogs and other smaller animals were killed or lamed by these high frequency waves.

It was found that the main reason for the destructive action of ultrasound is formation of gas bubbles by cavitation. (Cavitation is the presence of hollows or cavities in the liquid formed by the tremendous pressure difference existing between the crest and the trough of the sound wave.)

Furthermore as regards bone it appears that the cavitation effect can produce actual destruction of bone substance. Concentrated ultrasonic radiation may well produce osteoporosis of the destructive type that is similar to that resulting from callosal disease except that it is much more diffuse in type.

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Defects in Matrix Calcification

OSTEOMALACIA AND RICKETS

Introduction. There are frequent references in the literature to both rickets and osteomalacia. It would appear that they are two different diseases; actually this is not true. They are the same disease process as it occurs at different ages.

The basic process is an amineralization or a demineralization. When the epiphyseal plates are still open the greatest changes will be at these locations for here is the most active bone growth. The whole skeleton is affected but when the preponderant change is at the epiphyseal ends the process is termed rickets (Figs. 186 to 192).

In the adult when the centers are fused the whole skeleton is affected. It will require much longer to manifest an effect. But the disease is precisely the same and therefore while the authors discuss rickets in this chapter the reader must keep in mind that the whole problem is the same for osteomalacia.

Any cause listed here for rickets can in the same way produce osteomalacia. Any treatment effective for one is effective for the other.

Historical Notes. It is of interest to discuss the origin of the term rickets and primarily of the term infantile rickets the form which was of course described by the earlier medical men.

The term rickets appears to have originated from the word *ricket* in the Dorset dialect Skeels, however considered that it originated from an old English word *wick* meaning "to twist" and some have felt that it came from the old Anglo-Saxon *rieg* signifying a protuberance. Whatever the interpretation it is apparent that the word originated from English sources. English

the term rickets was accepted by G and so it has continued in the English literature. Its English origin is indicated by the German term "Die Englische Krankheit" (the English disease).

It is evident that because of the nature of this disease description of would not be found in the ancient or subtropical worlds. Sunlight the strong and the people are exposed uniformly from birth on. Converse northern latitudes there may not be adequate sunlight. Furthermore more cold is worn which cuts off still more radiation. Therefore in these areas the disease was recognized and was described.

The Egyptian and the early Greek apparently did not describe this condition. Findlay¹ searched in medical papyrus the archeologic records of Ebers, Brugsch and still found no clear description. G. Elliott Smith has gone as far as to say that clear unmistakable evidence of rickets has not been found in the bones in any cemetery of Egypt or Nubia.

Hippocrates wrote what was considered by many to be a clear-cut description of rickets in his chapter on joints in a collection in the Loeb Classical Library. The description is clearly that of the deformity of the spine and the chest which better tuberculosis of bone.

The Romans appear to have found evidence of this disease long before its discovery in England. Soranus of Ephesus an obstetrician and pediatrician who practiced medicine in Rome between the first and the second centuries A.D., is cited by Heus² with a clear-cut description of a rachitic state. It is referred to in a treatise entitled "How Must One Teach Children?"



FIG 186 Infantile rickets. Both hands and wrists. Anteroposterior view. Untreated rickets shows osteomalacia of the lower ends of the radius and the ulna, irregularity and cupping of the metaphyses with no condensation, widening and malacia of the metacarpals and the phalanges. All these findings indicate active advanced rickets.

When a child attempts to sit or stand, one must aid its movements. If it sits too early or too long it will tend to become deformed as the vertebral column bends due to the softness of the bones. If it stands or walks too early the legs (especially the thighs) will become crooked.

Galen referred to rickets in his work *De Morborum Causis*. For many centuries

thereafter there were no further important medical writings on this disease. In the sixteenth century Theodosius of Bologna described a pale infant aged 17 months, who could not move or sit, who could not hold his head erect and also showed a lower dorsal gibbus and a marked lateral curvature; this could well have been rickets.

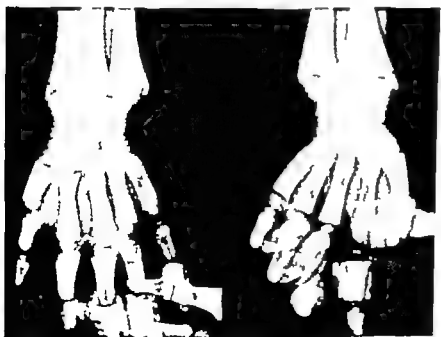


FIG 187 Infantile rickets. (Same patient as Fig 186 but now on antirachitic therapy.) Both hands and wrists. Anteroposterior view. Marked cupping and broadening of the metaphyses is evident. The presence of sclerotic margins in the metaphyses, the narrowing of the epiphyseal plates and the smooth contours of the epiphyseal centers indicate healing reaction.

FIG. 188 Infantile rickets. Both hands and wrists. Anteroposterior view. Active untreated rickets is present. Severe osteomalacia is observed throughout the wrists and the hands. There are widened osteoid zones at the epiphyseal plates. The epiphyseal centers are practically invisible.



Then in 1609 Guillemeau in a treatise on "Diseases of Infants and Children" described rachitic deformities.

It must be considered at this point that much confusion must have existed in early times because of the concurrent presence of both rickets and scurvy. Since these often occurred in the same patient with similar seasonal variations, they were not easily differentiated by the clinicians of those early days.

The first complete report and clear-cut description of this disease was published in England by Whistler² in 1645. In 1650 however the best and most thorough report of scientific value was published in Latin by Glisson.⁴ Glisson believed that this was a new disease which had become apparent only for the past 30 years in the counties of Dorset and Somerset in England. Following this time it was related to other places—to London to Oxford to Cambridge and to

FIG. 189 Infantile rickets. (Same patient as Fig. 188 now healing on antirachitic therapy.) Both hands and wrists. Anteroposterior view. Note that osteomalacia is improved in the shafts of the radius, the ulna, the metacarpals and the phalanges. The epiphyseal plates are narrowed to approach normal. The cupping of the metaphyses is reduced markedly. Sclerosis is observed at the base of the formerly cupped areas.





FIG 190 Infantile rickets. Knee. Anteroposterior view. There is marked irregularity of the osteoid zone of the epiphyseal plates with cupping of the metaphyses. There are irregularity, hardness and osteomalacia of the epiphyseal centers.



FIG 191 Infantile rickets. (Same patient as Fig 190) Knee. Anteroposterior view. This slightly different view shows marked cupping of the upper fibula metaphysis.

almost all the southern and the western parts of the kingdom.

Despite earlier medical description of this disease it is certain that the scholarly and complete description of rickets started with Francis Glisson and as is seen so commonly his clear report was but the beginning of many subsequent reports on this

condition. His clinical descriptions of deformities and the changes typical of this disease were most clear. Glisson also differentiated infantile rickets from infantile scurvy. Unfortunately like his contemporaries he was not a modern physiologist. Glisson as other medical men of his time, was dominated by the old humoral concept and in this way he indicated his theory of



FIG 192 (Top) Infantile rickets. (Same patient as Fig 190) Knee Anteroposterior view After antirachitic therapy the changes seen in Figures 190 and 191 have regressed.

FIG 193 (Bottom) Cellac disease (Figs. 193 to 195 from Dr Eugene P Pendergrass) White female, 16 months old. Right upper extremity and right leg. Anteroposterior view (June 26 1941) The bones of the upper and the lower extremities show marked demineralization with associated soft tissue atrophy. The absence of severe rachitic stigmata which might be expected in the presence of so much presumed osteomalacia in a growing infant argues for the possibility of an associated protein deficiency. One may assume therefore that there may be a large osteoporotic component in this case.



the etiology of the disease. He said: "Rickets is a cold distemper that is moist and consists in a penury, paucity and stupefaction of spirits." So we find only an excellent and detailed clinical description of the disease and pass on.

During the eighteenth century, medical literature simply accepted Glisson's views of etiology along with his more accurate description of the clinical course of the disease. However, in this period, increasing interest and numerous medical theses on this condition appeared. In the early eighteenth century, Boerhaave thought that this disorder was related to some venereal poison and the French strongly held to this theory, as they have in regard to so many disease states through recent times.

During the eighteenth century, more light

on this subject came about chiefly through more detailed clinical and necropsy findings such as areas of softening in the cranial bones of infants "cranial tabes" as described by the German Elsasser.

Kassowitz, of Vienna, drew attention to the characteristic seasonal incidence of the disorder. This of course is significant in light of its etiology.

In 1885 Pommer³ described the essential pathologic lesion as excessive osteoid tissue. It is of interest that the effect was considered by him to be the cause for we under



FIG 194 Celiac disease. (Same patient as Fig 193 now 19 months old) Treatment consisted of high-protein and high-calcium intake. Both upper extremities. Anteroposterior view (Sept. 13 1941) General demineralization of the long bones is still present. There has been definite increased density of the diaphyseal ends of the long bones. This probably results from the increased supply of calcium made available by treatment which has localized at the growing ends of the long bones.



FIG 195 Celiac disease. (Same patient as Fig. 193 now 19 months old) Both knees and legs. Anteroposterior view (Sept. 13 1941) The post treatment bands of increased diaphyseal density are noted in the long bones of the lower extremities.

stand now that the excess osteoid is present only because the rachitic process prevents the calcification of osteoid. But the benefit from this error was the foundation of histologic studies of this disease.

Pommer also described rickets and osteomalacia as identical pathologic processes.⁶ This work was confirmed by Schmorl⁶ in 1909 and later again by Looser.⁷

Only in the twentieth century of course has true understanding of this disease process come about. Knowledge of organic and inorganic chemistry of hormones and vitamins has clarified the thinking and the methods of analyzing this disorder.

It is to be expected that earlier medical authorities could only have been able to discern very advanced forms of this disease. It would have been impossible for them to have differentiated the very mild phases without the x-ray pictures and the biochemical studies available to the physician of today. Fortunately better methods of diag-



FIG. 196 Rickets associated with congenital atresia of the biliary tract. (Figs 196 to 200 from Dr. Paul Morris and Dr. Richard J. Chodoff.) Colored male infant. Congenital icterus. Studies revealed obstructive jaundice with signs of liver damage. In January 1952 exploratory laparotomy was carried out. Anastomosis of the jejunum and the hepatic duct stump was performed. Anteroposterior view of lower extremities (March 1952 at 7 months). Evidence of florid rickets with demineralization of all the bones is seen. The knee and the hip epiphyseal centers are barely visible.



FIG. 197 Rickets associated with congenital atresia of the biliary tract. (Same patient as Fig. 196.) Parenteral vitamin D as well as an oral preparation was given. The liver damage began to reverse on biochemical studies. Bile flow was successfully re-established following surgery. Both knees and legs (July 1952 at 11 months). The bones show better mineralization. Metaphyseal sclerosis is present, indicating healing of the rickets. The epiphyseal centers are shown more clearly than in Figure 196.

nosis and understanding of the etiology of this process have produced efficient methods of prophylaxis and treatment. So now the modern physician rarely sees this condition except in a very mild state or in aberrant form usually associated with kidney disease, gastro-intestinal disturbances

of the celiac type, and liver or biliary tract disease (Figs 193 to 200) (See Table 8 p. 469).

Pathogenesis. Rickets is a metabolic disturbance on a deficiency basis which affects the skeleton. Clinically it is a generalized condition with characteristic changes in bone structure manifest by enlargement of the epiphyseal junctions. Later in the disease softening and bending of bones, stunted growth, abnormal proliferation of epiphyseal cartilage and formation of osteoid tissue

occur. The physiologic growth of long bones is replaced by a disordered growth, in which there is disruption of normal boundaries between the usual orderly zones. In place of lamellated bone there occurs an unlamellated tissue or so-called osteoid tissue that is uncalcified.

Modeling of bone does not occur because of the difficulty of reabsorption of uncalcified matrix or osteoid. The medullary cavities show highly vascularized connective tissue containing lymphocytes and no fat cells.

Pathology The pathology of rickets may be summed up as follows:

There is continued proliferation of the epiphyseal cartilage which, however, is slightly less active than the normal state. This proliferating cartilage grows in columns many times the normal length. As

the disease continues and these continue to grow in this fashion distalization occurs and the column pattern with the cells forming whorls.

The deficiency rests in the failure of cartilage to calcify in the provision. For it must be remembered that the calcified cartilage islands are a nidus of formation in the normal pattern. In disease, however, these islands of cartilage persist as uncalcified cartilage. They are surrounded by a sea of ingrowing tissue which is uncalcified and osteoid.

Similar osteoid zones become deposited around all pre-existing bone trabeculae. These osteoid seams are not calcified. As they widen they accentuate the separation of the old bone trabeculae which are thinned by the disease process.

Osteoid is laid down in like pattern.



FIG. 198. Rickets associated with congenital atresia of the biliary tract. (Same patient as Fig. 196.) Anteroposterior view of both forearms and hands (May 1952, at 9 months). Active rickets is present, as evidenced by demineralization, by metaphyseal cupping and fraying and by the absence of epiphyseal centers in the wrist.

walls of the haversian systems. It is also laid down both subperiosteally and endosteally so that widening of the transverse diameter of bone involved occurs.

Cupping is evident at the epiphyseal ends because the changes in these locations are greater than they are in the shafts. Endochondral ossification is slowed in these areas in relation to that which occurs in the diaphyses.

In chronic long standing rickets the entire bone may become involved by this porotic demineralization process. In the adult when growth is finished the picture is called osteomalacia. Widespread softening of the entire bony structure occurs in this instance. With bone structure softening there is susceptibility of the involved bone

to deformity through weight-bearing and to some extent through muscle pull.

The skull shows some changes because it develops by membranous bone formation and the lack of calcification of osteoid allows for considerable overgrowth. Eventually when healing occurs we have the prominences that are evident in this disease.

Etiology The classical type of rickets is the infantile form secondary to vitamin D deficiency. There is also that group of rachitic conditions associated with kidney dysfunction the acidotic or Albright Butler group. In this instance there is a loss of calcium as additional fixed base in the urine. There is not enough ammonia available and the body is forced to use calcium to combat the acidosis. Fanconi rickets is

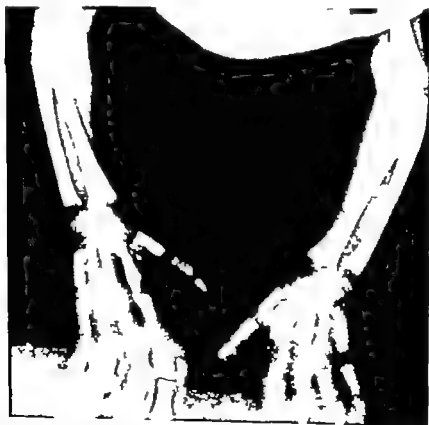


FIG. 199 Rickets associated with congenital atresia of the biliary tract. (Same patient as Fig. 196.) Anteroposterior view of both forearms and hands (July 1952 at 11 months). This is the same time as lower extremity film shown in Figure 197. Healing reaction has occurred. There are still some increased metaphyseal density and minimal residual cupping.

the result of a defect in kidney function which results in glycosuria, cystinuria and excessive phosphorus excretion. These renal tubular forms of rickets and osteomalacia are discussed in greater detail in Chapter 12 (Figs. 223 to 229).

We also have so-called hepatic rickets associated with liver dysfunction as well as rachitic changes associated with idiopathic steatorrhea or other parts of the celiac syndrome.

There is also vitamin D resistant rickets due most probably to a hereditary inability to utilize vitamin D. This is covered in detail on page 270.

It should be emphasized that the pathologic changes in all rachitic or osteomalacic processes are much alike no matter what the cause of that particular rickets or osteomalacia. However, as time has gone on, nu-

merous types of rickets have been described especially more recently where the pattern has not always been defined clearly. At this point a pattern should be defined. The term rickets is primarily of historical interest. It no longer describes a presumed specific condition but rather a picture of x-ray and histologic changes in bone due to derangement of the normal biochemical processes affecting the mineralization of the skeleton.

This definition is necessary since modern terminology includes in the family of rickets diseases which are not due to avitaminosis D. Such conditions nonetheless, may show a characteristic clinical, histologic and roentgenographic picture.

Normal bone is in a state of constant flux. It dies. It reabsorbs and new tissue reforms. Growing bone undergoes precisely the same processes as the adult form except



FIG. 200 Rickets associated with congenital atresia of the biliary tract. (Same patient as Fig. 196.) Following full re-establishment of bile flow and regression of liver damage the child no longer required parenteral vitamin D. Oral maintenance dosage of 1,000 units daily was adequate. Anteroposterior view of both forearms and hands (September 1952 at 13 months). Complete healing of the rachitic process has occurred. These are now two sharply defined carpal centers. Bone density is normal.

for the fact that the growing portions show markedly concentrated bone formation. Disease therefore will be more apparent in the epiphyseal areas. Osteoid tissue is a product of the osteoblast and this tissue does not enter into normal bone structure unless it becomes calcified. It is the only bone component which does become calcified. Calcified osteoid gives strength to bone and because it is easily reabsorbed allows for bone modeling. That means it allows for shaping of bone to normal configuration and so that there is a normal relationship of cortical cancellous and medullary bone. Derangement of calcification of osteoid in growing bone results in a rachitic state.

So anything that interferes with or prevents calcification of osteoid results in rickets. This condition may be a fault in supply of minerals to osteoid or a fault in utilization of any single or combined essential osteoid calcifying material.

There are at least three essential substances for normal ossification of bone. There may be more but these substances singly and in combination must be present in adequate amount for normal bone development to continue. The intake and the absorption of these substances must be adequate. Furthermore even after absorption they must be transported to the bone and properly utilized by the uncalcified osteoid. These substances are calcium, phosphorus and vitamin D.

Various types of rickets have been described but on analysis they simply represent something that has gone wrong in getting the required material or materials to the osteoid. Such a breakdown in supply of essential substances may occur at any point whether in the intake, in the absorption or in the utilization of the material by the osteoid. Such a concept of course allows us to fit various forms of rickets into a clear cut pattern. In the final event a type of rickets occurs because events lead to a particular deficient state. Low-calcium rickets is associated with the following:

1 Lack of calcium intake

2 Lack of vitamin D to increase absorption of calcium through the gut

3 Lack of calcium absorption such as occurs in

A. Excess of phosphorus intake which results in nullification of calcium by production of insoluble calcium phosphates.

B. Abnormal liver function with resultant excess fatty acids and saponification of calcium by these fatty acids. Elimination therefore of the calcium from the bowel in the form of soaps.

C. Excess oxalate intake which precipitates calcium in the gut.

4 Renal acidosis of the Albright Butler type where calcium is utilized in place of ammonia for base. This loss of calcium may be reflected in parathyroid hypertrophy and secondary hyperparathyroid symptoms.

5 Primary hereditary renal tubular disease causing Fanconi rickets may be considered here as occurring on a hypophosphatemic basis not associated with hypercalcaemia. We mean that the basic problem is hypophosphatemia probably associated with increased loss of phosphorus in urine.

The characteristic acidosis of the Fanconi type is the result of increased urinary loss of fixed base. This is secondary to the increased excretion of organic acids such as amino acids, lactic acid and beta hydroxy butyric acid. Calcium is lost as part of fixed base required to compensate for excess organic acids excreted in the urine. The excess calcium excretion in this syndrome may cause some secondary hyperparathyroidism. This will further aggravate the hyperphosphaturia and accentuate the hypophosphatemia.

There is also an associated loss of glucose and cystine in the urine secondary to tubular disturbance.

Low phosphorus rickets or so-called infantile rickets, is the usual form of the disease and occurs in association with the following:

1 A lack of adequate phosphorus intake

2 An excess phytin intake which nullifies phosphorus and neutralizes it

the result of a defect in kidney function which results in glycosuria, cystinuria and excessive phosphorus excretion. These renal tubular forms of rickets and osteomalacia are discussed in greater detail in Chapter 12 (Figs 223 to 229).

We also have so-called hepatic rickets associated with liver dysfunction as well as rachitic changes associated with idiopathic steatorrhea, or other parts of the celiac syndrome.

There is also vitamin D resistant rickets due most probably to a hereditary inability to utilize vitamin D. This is covered in detail on page 270.

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FIG. 200 Rickets associated with congenital atresia of the biliary tract. (Same patient as Fig. 196.) Following full re-establishment of bile flow and regression of liver damage the child no longer required parenteral vitamin D. Oral maintenance dosage of 1,000 units daily was adequate. Anteroposterior view of both forearms and hands (September 1952 at 13 months). Complete healing of the rachitic process has occurred. These are now two sharply defined carpal centers. Bone density is normal.

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- 2 Lack of vitamin D to increase absorption of calcium through the gut

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There is also an associated loss of glucose and cystine in the urine secondary to tubular disturbance.

Low-phosphorus rickets or so-called infantile rickets is the usual form of the disease and occurs in association with the following:

- 1 A lack of adequate phosphorus intake
- 2 An excess phytin intake which nullifies phosphorus and neutralizes it

- 3 A lack of phosphorus absorption
- 4 An excess of calcium so that phosphorus is nullified.
- 5 A lack of vitamin D to increase absorption of mineral through the gut.
- 6 An excess of any of the following elements which will nullify dietary phosphorus: magnesium, beryllium, strontium, aluminum, cadmium, thiocyanate and gallium.

To repeat we have seen therefore that rickets is a derangement of growing bone. It becomes manifest predominantly in the epiphyseal or growing membranous portions of bone due to a lack of vitamin D from either sunlight or diet. It also occurs if there is no calcium or phosphorus for deposition in the bone matrix.

The conditions affecting the supply of these important materials to produce calcified osteoid may therefore be very serious. For practical reasons we have indicated the broad groups above. Other groups can also be postulated when one considers the underlying mechanism as simply failure of calcification of osteoid. There is no doubt also that further types of rickets will be described in the future.

From the point of view of therapy, differentiation is important because as an example, we may have what appears to be typical vitamin D deficiency rickets yet it may be due to excess phytin intake. It may also be associated with some other noxious elements that may prevent the absorption of phosphorus. There may be an inadequate vitamin D intake or there may be simply a hereditary inability to utilize vitamin D. All of these processes must be considered. Differentiation as to cause is essential for effective treatment.

One must be alert to the possible simultaneous occurrence of both active rickets and active scurvy. When this occurs the signs of scurvy may predominate. The vitamin-C deficiency prevents osteoid formation in scurvy which in turn is not reflected by an elevation of alkaline phos-

phatase. Elevation of alkaline phosphatase is usually observed in classical rickets.

The roentgenographic picture of rickets may also predominate. However, cupping of the epiphyseal ends of bones and other signs of rickets will be present although not dominant. Combined treatment was indicated.

Treatment. It is of interest that the first treatment for the vitamin D deficient infantile type of this disease was more than 100 years ago.

Mozolowsky⁸ indicated that T. A. Laycock, an English physician first directed attention to the curative effect of sunlight on rickets in 1890. He also pointed out that rickets was prevalent in geographic areas where there was little sunlight and that it was unknown or comparatively rare where sunshine was abundant.

However, the Polish physician Keckl¹⁰ in his book on *A Physical Education of Children* written in 1822 says in chapter on "English Disease" that

If the parents financial status permits best to take the children out into the open air and keep them as much as possible in the open and pure air. If not at least, they should be carried about in the open air especially the sun the direct action of which on the bodies must be regarded as one of the efficient methods for the prevention and cure of this disease.

Cod liver oil was recognized to be curative but was often given in Germany without supplementary phosphorus and the effects attributed to phosphorus even until the year 1900. On the basis of work in experimental animals, Mellanby¹¹ and McCollum¹² described rickets as a deficiency disease. In 1914 the first important demonstration of the curative action of ultraviolet lamp rays was established.¹³ In 1921 roentgen evidence of healing in rickets following the use of liver oil was reported upon.¹⁴ The effective ultraviolet radiation upon fat-containing foods^{15, 16} followed Hulschinsky's report upon cure of rickets by ultraviolet radi-

plus the knowledge that cod-liver oil was also effective.¹⁴

In 1917 Hess and Windaus¹⁷ and Rosenheim and Webster¹⁸ discovered that the active factor in the ultraviolet irradiated preparation was irradiated ergosterol which is now known as calciferol.

PRESENT REGIMEN FOR TREATMENT OF VITAMIN D DEFICIENT RICKETS Treatment must be considered from two points of view: first, the underlying fault; second, any deformities that may have arisen as a result of this disease process.

The primary problem usually is due to a fault in supply of vitamin D. It may result from lack of sunlight or lack of vitamin D in food or both.

The vitamin-D intake must be raised to or above the full normal requirement. The normal requirement for children is 400 to 800 units of vitamin D per day. For treatment of active rickets, 8 000 to 10 000 units per day is indicated. This should be continued until complete healing of the rickets has occurred. Then the dose may be dropped to 400 units daily for infants and up to 800 units for older ages (up to 20).

The precise number of vitamin-D capsules or drops of vitamin D concentrates required cannot be stated uniformly. Consider 10 000 units as the top desired therapeutic dose. The answer is obtained by simple computation based on study of the vitamin D content of the preparation. It is well to make certain that the therapeutic dose required in treatment of active rickets, not the recommended prophylactic dose, is given.

Do not overdose for harmful effects may result. Overdosage of vitamin D will not ensure a quicker cure.

Do not underdose for too little vitamin D in active rickets will depress the parathyroid without increasing calcium absorption via the gut. It will not be enough to increase renal phosphorus excretion. So small doses of vitamin D by diet or sunlight in active rickets may cause tetany with hyperphosphatemia and hypocalcemia with continued

elevation of alkaline phosphatase. This tetanic picture was quite common when rickets was more prevalent and the above mechanism not understood.

It is important to remember that disproportions of calcium and phosphorus in intake will be minimized in the presence of high intakes of vitamin D.

In addition to the therapeutic 10 000 units of vitamin D per day, the regimen should include adequate amounts of other vitamins, particularly vitamin C. This is easily accomplished with present multivitamin preparations. A simple formula is pure vitamin D concentrate 9 000 units per day and a multivitamin capsule or drop dosage of 1,000 units of vitamin D daily, which will also contain generous prophylactic doses of vitamin C and other vitamins.

Mixed clinical scurvy and rickets will require additional ascorbic acid so that 500 mg. daily is given until healing has resulted.

The diet should be adequate for protein, carbohydrates, calcium and phosphorus (see Table on p. 78). Minimum requirement of protein for maintenance is 3.5 Gm. per kg. for infants down to 1.0 Gm. per kg. for adults. Therapeutic dosages should be higher. Total calcium intake must be above the maintenance level, which is 0.6 to 1.0 Gm. daily in the first year of life and thereafter. Phosphorus requirements are higher than calcium. Foods containing calcium in adequate amounts usually yield proper phosphorus intake. Moreover, adequate animal protein will also include substantial amounts of phosphorus.

Meat, seafood and dairy products are the major food sources of required phosphorus, calcium and protein.

For healing of rickets, additional calcium may be given. A recommended form is calcium lactate or calcium gluconate, 0.5 to 3.0 Gm. three times daily.

A similar dose of Ca_2HPO_4 , dicalcium phosphate, is also useful and may be utilized in place of the calcium lactate or gluconate.

In addition, substances that may interfere

with calcification either by affecting absorption or by preventing utilization of the calcium, the phosphorus or the vitamin D should be reduced or eliminated

For example Mineral oil prevents vitamin D absorption

Phytins decrease calcium available for absorption.

Oxalic acid nullifies calcium for use even after absorption.

Aluminum hydroxide gel prevents phosphorus absorption

CORRECTIVE MEASURES FOR DEFORMITIES.

Bulbous bony enlargements may partially or occasionally totally recede under adequate therapy particularly if the therapy is started early

Spinal kyphos partially resolves complete resolution cannot be obtained easily Any surgery required would be more radical than the deformity justifies

Once formed, pelvic distortion will not correct and again surgery to improve the outlet in women is not justified Rather cesarean section should be done if measurements indicate the desirability of this procedure Deformity of the pelvis does not produce other disability as a rule but can be associated with protrusion of the acetabulum (Otto pelvis) and coxa vara deformities

These latter deformities may require complex orthopedic surgical care Otto pelvis may be treated by arthroplasty of the hip with bone-chip placement to reduce the depth of the acetabulum.

Subtrochanteric osteotomy with appropriate metallic fixation so that the upper fragment can be brought away from the side of the pelvis is desirable in severe rachitic coxa vara deformity One should not abduct the shaft to line up with the femoral head and the trochanters The reason is that this latter maneuver will not permit proper adduction of the proximal fragment in relation to the hip joint In fact if the shaft has

healed to the proximal fragment in marked abduction and thus is aligned with proximal fragment which is itself in marked abduction as to be a part of original coxa vara deformity then after at adduction will only cause a shift of bowing force to the osteotomy area. plastic zone will itself become the point of deformity with recurrence of the coxa vara If the head and the neck are brought away from the pelvis this vicious sequence can be avoided.

Bowing of the lower extremities or knee deformities may be treated as follows

Before age 4 and up to 2 inches of deformity (the distance between the malleoli when the knees touch in knock knee) distance between the femora when the tibiae touch in bowlegs) cases progress under antirachitic therapy and with shoes inner heel and sole wedges for knock knee outer heel and sole wedges for bow legs

Before age 4 and above 2 inches of deformity we use antirachitic measures and braces. Long leg braces with pressure pads and no joints at the knee are preferred.

After age 4 and above 2 inches of deformity the following can be done

1 Bone-softening diet with strontium carbonate low vitamin D and phosphorus intake (Nachlas and Shelling) Then massage and manipulative correction of deformed softened bone Then antirachitic regimen to follow This method was used at Johns Hopkins Hospital with fair success in early 1930's The time required for the result the persistent concentration of strontium in the blood and the general osteoporosis with head deformity make surgery more desirable and definite in these cases

2 Surgery and antirachitic regimen. This would include proper osteotomies. Such osteotomies must be done close to the site of maximum deformity Osteotomies for angular deformities fall into 3 gross categories

A. A collapsing osteotomy. In this type a proper-sized wedge is removed from the convex side. When this space is closed the deformity is corrected. This results in some shortening of the bone.

B. An opening osteotomy. In this type the cut in the bone is made in the concave side. When this is opened the deformity is corrected. This results in some lengthening of the bone. Bone chips or blocks plus possible additional skeletal fixation must be used to maintain the opened wedge.

C. Curved plane osteotomy. In this instance a semicircle is cut at 90° to the plane of deformity. When the cut is com-

pleted with drill holes and the use of a thin osteotome the deformed bone is straightened. This results in no change in length.

RICKETS OR OSTEOMALACIA DUE TO FAULTY ABSORPTION. This group is now classified as steatorrhea because of the foul, fatty, frothy stools. This is the same group as the hitherto described celiac syndrome, so-named because of the obvious enlargement of the belly. The recent classification has been on the basis of etiology. Subgroups include

1. Fat intolerance of the premature infant.
2. Idiopathic steatorrhea of the young

TABLE 6. DIFFERENTIAL DIAGNOSIS OF THE CELIAC SYNDROME*

	CELIAC DISEASE	STARCH INTOLERANCE	PANCREATIC DEFICIENCY	INFANTILE STEATORRHEA
Age of onset	10 mos. to 5 yrs.	3 to 12 mos.	Birth to 4 mos.	Birth to 6 mos.
Dietary intolerance	Fat and carbonyl drate	Starch	Fat and starch	Fat
Respiratory infections	Upper respiratory infection	Repeated upper respiratory infections, bronchopneumonia	Chronic bronchitis, bronchiectasis	Upper respiratory infections
Growth	Retarded or normal	Usually normal	Retarded	Normal or retarded
Abdomen	Large	Moderately large or normal	Large	Normal or moderately large
Watery diarrhea	With crises	Occasionally	No	Yes
Hydrochloridty	Yes	No	No	Yes
Anemia	Yes	Yes	No	?
Vomiting	During crisis	Occasionally	Unusual	Occasionally
Intestinal motility	Markedly abnormal	Abnormal in most cases	Abnormal	?
Stools	Large, greasy, foul	Large, frothy, foul	Large, formed, foul	Watery, pale
Stool fat	High	Normal	High	High
Stool starch	Normal or slightly increased	High	High	Normal
Duodenal enzymes	Normal, decreased during dehydration	Low amylase	Absent	Normal, decreased during dehydration
Serum lipids, cholesterol	Low	Normal	Low	Low
Glucose tolerance curve	Low or flat	Normal or low	Normal or low	?
Serum protein	Normal or low	Normal	Normal	?
Vitamin deficiency	Various	?	Fat-soluble vitamins	?

*From Andersen and Hodges: *Practical Pediatrics* (J. Brennerman, Ed.) vol. 1, chap. 29, Hagerstown, Md., Prior.

child (sometimes referred to as cellac disease) (Figs 193 to 195)

3 Sprue, both tropical and nontropical in adults. Actually these appear to be alike and are differently termed only because of geographic location.

4 Cystic fibrosis of the pancreas in the infant and the young child

5 Chronic pancreatitis and pancreatic duct stones producing obstruction in the adult

6 Obstructive lesions of the biliary tract (Figs. 196 to 200)

7 Miscellaneous group

A Infestation with *Giardia lamblia*

B Partial gastrectomy

C Lymphosarcoma.

D Intestinal tuberculosis and Hodgkin's disease affecting the mesenteric lymph nodes

E Intestinal lipodystrophy

The mechanism of all these conditions as related to rickets or osteomalacia is the same. These diseases from the authors viewpoint have the common denominator of faulty fat absorption.

Two mechanisms may work in these conditions to interfere with calcium absorption. First faulty fat absorption infers poor absorption of fat soluble vitamins especially vitamin D. Second fatty acids combine with calcium to form insoluble soaps which are lost in the feces. Therefore, the skeleton will be deprived of both calcium and vitamin D and this will result in rickets or osteomalacia the same as occurs when supply of these materials is inadequate.

Diagnosis is important, for treatment is most effective with proper appreciation of the underlying disease.

All of these diseases are characterized by an increase in total fat in the stool, a flat vitamin A tolerance curve with oily preparations and skeletal manifestations of rickets and osteomalacia. These diseases do vary in some respects and therefore can be differentiated from each other.

Treatment of Rickets and Osteomalacia

from Faulty Absorption This requires adequate absorption of vitamin D and calcium and correction of the primary disorder if possible.

1 Vitamin D may be given in aqueous form with wetting agents parenterally or by ultraviolet irradiation. The dose should be about 10,000 units daily with amounts depending upon the preparation used.

2 Adequate amounts of calcium and phosphorus should be administered. Skim milk up to 1 quart a day, cottage cheese 2 to 6 ounces daily, $(\text{Ca}_3\text{HPO}_4)$ dicalcium phosphate wafers, calcium lactate or calcium gluconate 0.5 to 3 Gm. three times daily.

3 Treatment of the underlying cause.

A Cystic fibrosis of the pancreas and chronic pancreatitis—pancreatin, high protein rich in lean meat, high carbohydrate fat free diets. Bananas are excellent as part of the regimen. Special high-protein milk formulas are used in infants. Antibiotics are used for the pulmonary infections.

B In idiopathic steatorrhea in children and in sprue in the adult, a diet similar to that above without pancreatin is prescribed. In those cases in which there is a macrocytic anemia vitamin B_{12} and/or folic acid as well as crude liver extract, 2 cc. I.M. each 2 days are required. Those with associated hypochromic anemia require iron in addition. Those with decreased prothrombin time require vitamin K. In all these cases but particularly for formula fed infants high-protein milk is valuable.

C Disturbances inferring blockage of the pancreatic or the bile ducts ought to have appropriate surgical treatment.

D Conditions due to giardiasis may be treated with arsenic and iodine compounds also with Atabrine and chloroquine. The arsenic compounds include carbarsone and Stovarsol.

VITAMIN D RESISTANT RICKETS

(Syn Refractory rickets.)

Definition. This is a rickets characterized by biochemical and clinical findings similar

to those of infantile rickets. It differs from ordinary vitamin D deficiency rickets in that it develops in individuals receiving the usual prophylactic doses of vitamin D.

It does not respond to standard oral or parenteral therapeutic intakes of this vitamin.

Its control requires a high vitamin D level by either parenteral or oral administration. The doses required may be enormous from 50,000 to 500,000 I U daily or more.

Historical Notes. In 1937¹ a case of late rickets due to a resistance to the action of vitamin D was reported. This patient had had rickets throughout his life despite vitamin D prophylactic levels normally considered adequate.

The chemical findings were similar to those of the usual forms of vitamin D deficiency rickets. These included normal serum calcium, low serum phosphorus and high serum phosphatase and increased fecal output of calcium and phosphorus. 450,000 I U of vitamin D daily corrected the chemical aberrations. Smaller doses had no appreciable effect. The primary guide was the effect upon fecal calcium excretion. The above level of vitamin D proved to be necessary to bring about absorption of calcium via the gut. This thereby reduced the calcium excreted in the feces.

These authors concluded that there was a resistance in this patient to the action of vitamin D wherever this primary action occurs.

Since this initial presentation other reviews and case reports have appeared. None has shed much light on the etiology. All have emphasized the high oral doses of vitamin D required to control the process from 50,000 to 500,000 I U daily.²

A most complete treatise on both the biochemical and the orthopedic management of this disease emphasizes the familial incidence and the chronicity of the ailment with production of dwarfism. Furthermore deformities on an osteomalacic basis were found to recur in adult life.³

Etiology. Explanations for this disease

fall into 3 gross categories. The first and simplest is lack of absorption of orally administered vitamin D. Albright et al.¹ very early appear to have shed doubt upon this explanation. They reported the need for large doses of vitamin D to produce a remission. This did not appear to vary whether the oral or the parenteral route was used.

A second explanation, and one favored by Albright,¹ is that the defect lies at the point of the primary action of vitamin D. It is postulated that an elevated threshold exists for response to vitamin D. When this level is exceeded, a normal action of vitamin D will result. To reach this threshold enormous doses of vitamin D are required. More over once the threshold is passed there is only a relatively short step to toxicity; therefore, care in control of dose is required.

A third view⁴ is that the defect lies in the renal tubule. This infers a faulty reabsorption of phosphorus via the tubules. The data upon which this view rests is the relatively increased urinary phosphorus excretion in relation to a lowered serum-phosphorus level.

This is not fully reasonable in view of the fact that long-standing rickets of this type shows hyperparathyroidism. The increased urine phosphorus excretion and the lowered serum phosphorus are expected findings in hyperparathyroidism.

Furthermore this conclusion postulates a very special type of tubular disturbance. It implies a sort of forme fruste of Fanconi's syndrome which is helped by vitamin D in massive doses. True Fanconi's syndrome does not appear to be affected by vitamin D in any dosage.

The true etiology, therefore in the authors' opinion is still unknown.

Until the paper of Pedersen and McCarrroll,⁵ the disease was considered very rare with only about 30 cases reported. These authors list 25 cases and the inference is that many cases are available for metabolic study in crippled children's homes.

Clinical Characteristics. These cases are similar in clinical signs to infantile rickets,

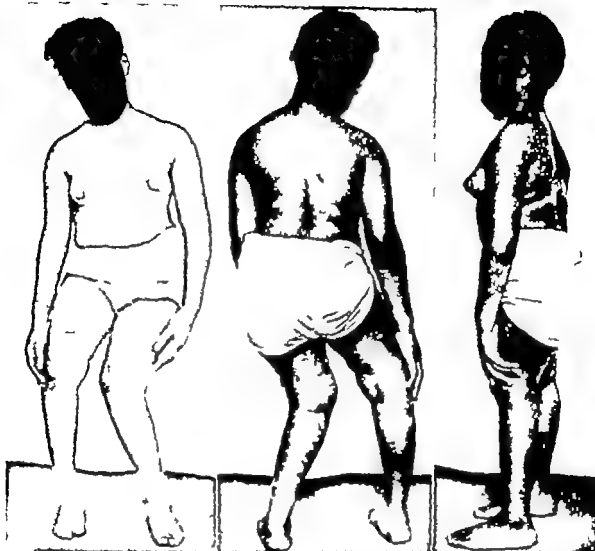


FIG. 201 Vitamin D resistant rickets. Colored female, 11 years old. This child was first seen at the age of 3 years with what appeared to be a severe bilateral congenital or infantile coxa vara. The vitamin D resistant rachitic state was not appreciated at this time. Bilateral subtrochanteric osteotomies were performed. Heavy Steinmann pins were used to control the upper fragment of each femur in order to pull it downward and away from the pelvis. Simple distal fragment abduction will not suffice to correct cervical coxa vara. See text on Page 268.

Following healing of these osteotomies this patient was lost to follow up until the age of 10 years at which time she presented dwarfism and multiple deformities particularly of the lower extremities. The possibility of vitamin D resistant rickets was now entertained and confirmed by biochemical studies as well as response to treatment with large doses of vitamin D. Initial biochemical studies revealed normal serum calcium, diminished serum phosphorus and elevated alkaline phosphatase. The urinary Sulkowitch reaction was negative. Note the dwarfism and the deformities of the lower extremities. The right thigh is badly bowed and twisted. Torsional changes are present in both legs.



FIG 202 Vitamin D resistant rickets. (Same patient as Fig. 201) Lateral view of skull (July 1954) The bone is excessively granular with prominent trabeculae. The inner and the outer tables are thin and contrast poorly with the diploë



FIG. 203 Vitamin D resistant rickets. (Same patient as Fig. 201) Both upper extremities. Anteroposterior view (April 1954) The bone trabeculae are coarse and spongy in appearance. The radial head epiphyses are condensed bilaterally. No long bone deformities are present.



FIG 204 Vitamin D resistant rickets. (Same patient as Fig. 201) Anteroposterior view of both hands and wrists (May 1954) Before treatment. There is pronounced demineralization with prominent trabecular pattern and cortical thinning. The distal ulna metaphyseal areas show cupping. Contrast with Figure 205

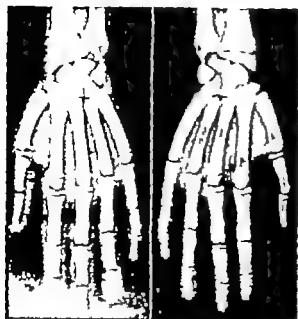


FIG. 205 Vitamin D resistant rickets. (Same patient as Fig. 201) The patient was placed on large doses of oral vitamin D. The initial dose was 50,000 units. This was increased biweekly by 50,000-unit increments with careful check of serum calcium, serum phosphorus and urinary calcium excretion. Stabilization occurred at 500,000 units which is being continued as a maintenance dosage. At this point the urinary Sulkowitch test is slightly positive and the serum calcium is normal. The serum phosphorus returned to normal on this regimen. A rise of serum phosphorus followed by a rise of serum calcium would be an indication for the reduction of vitamin D dosage to a lower maintenance level. See text for fuller discussion of this delicate balance between maintenance and toxic levels of vitamin D. Anteroposterior view of both hands and wrists (September 1954). After treatment. Compare with Figure 204. Distal ulna cupping has regressed. Bone mineralization is improved but is not yet normal after only a short period of treatment.

except that they represent a more long standing and florid type. There is a familial background of dwarfism and deformity in most cases. Similar hereditary dwarfism has been observed in achondroplasia as well as in multiple enchondromatosis (dyschondro-



FIG. 206 Vitamin D resistant rickets. (Same patient as Fig. 201) Dorsolumbar spine. Anteroposterior view (May 1954). The vertebral bodies are coarsely granular in appearance. The ribs are similarly demineralized. There is a right dorsolumbar scoliosis.

plasia) (Figs. 73 to 76 and 53 to 59). It is not surprising therefore that many dwarfs due to the more recently delineated vitamin D resistant rickets have been misdiagnosed as the other forms.

These cases show short stature based upon retarded epiphyseal growth particularly in adolescents and adults (Fig. 201). The epiphyses are enlarged and prominent with knobbing of the wrists and the knees, and rachitic rosary. Other features include Harrison's groove of the chest, prominent frontal bones, dorsal spinal kyphosis, coxa vara, knock knee or bowleg deformities (Figs. 202 to 210).

LABORATORY FINDINGS. These are similar to those of infantile rickets. They include normal serum calcium, diminished serum phosphorus and elevated alkaline phosphatase. Fecal calcium is increased, urinary calcium is lowered.



FIG 207 Vitamin D resistant rickets. (Same patient as Fig. 201) Anteroposterior view of pelvis and hips (April 1954) Before treatment. The trabeculae are granular and coarse. Active rickets is indicated by a zone of poorly calcified osteoid at the proximal femoral metaphyses and at the lesser trochanters bilaterally. The right femur is markedly bowed. Contrast with Figure 208.



FIG 208. Vitamin D resistant rickets. (Same patient as Fig. 201) Anteroposterior view of pelvis and hips (September 1954) After treatment. Compare with Figure 207. The bone mineralization has improved as indicated by the over all decrease in trabecular granularity. Particularly to be noted is the calcification of the upper and the lower femoral metaphyses and the lesser trochanteric apophyses. The rachitic pattern is now healing on massive vitamin D dosage.

ROENTGENOGRAPHIC FINDINGS. These are similar to those of severe rickets. There is widening of the epiphyseal lines with fuzziness at the metaphyseal end of the epiphyseal plate (Figs. 204, 205, 207 to 210).

In late cases the architecture of the entire skeleton is changed to show coarsened trabeculae, thinned compact bone and increased diameter of all bones. Furthermore roentgenograms show evidence of all the clinical deformities noted above (Figs. 202 to 210).

Bony ridges at the site of muscle attachments are increased in size. This results from muscle pull on incompletely calcified osteoid. The tissue raises as a result and when

finally calcified is observed to be of increased size.

Pathology. This is similar to that of infantile rickets. In view of the fact that no one has demonstrated the specific defect, the changes found will be primarily those of the skeleton. These are basically failure of calcification of osteoid and this is particularly so in the epiphyses of growing subjects. In adults the uncalcified osteoid will be widespread.

Treatment. This must be approached from two points of view. First the attack

upon the rachitic process second the attack upon the deformities

The rachitic process may be controlled by maintaining adequate levels of vitamin D. Simply to give large doses is not the answer. Dosage must be correlated with control of chemical disturbances. The reason is that the therapeutic level is very close to the toxic level. The toxic effect of vitamin D is primarily hypercalcemia and its side-effects including nausea vomiting abdominal pain drowsiness and even fatality. Hypercalciuria and metastatic pathologic calcification occur.

The most direct method of obtaining accurate control is to evaluate the fecal calcium output. When the vitamin D level is adequate the fecal calcium excretion will be come reduced from that level determined before the administration of vitamin D. This method carefully followed over three-day periods with gradually increasing doses of vitamin D will give the required dose for

optimal effect. However it is a difficult method to follow so a more practical one is to study the urine by the Sulkowitch test.

The rationale here is the indirect measurement of vitamin D action on intestinal absorption of calcium by checking urinary calcium. Fecal-calcium evaluation measures calcium absorption directly. As calcium is absorbed through the gut, the calcium in the feces becomes reduced by that amount.

However once calcium has become absorbed through the gut, it will go into the blood stream to be taken to bone and kidney. Increased absorption of calcium resulting from proper dosages of vitamin D will, therefore be reflected indirectly, in the urine. The urine will show increased calcium content. Therefore a gross but simple test like the Sulkowitch test will indicate, by means of relative increases in calcium excretion through the urine increases in calcium absorption through the gut. A very strongly positive Sulkowitch reaction will infer



FIG. 209 Vitamin D resistant rickets. (Same patient as Fig. 201.) Lateral views of right knee. Before and after treatment. The pretreatment film on the left shows the diagnostic metaphyseal rachitic band of demineralization. This is calcified on the later film. The bone trabecular pattern is less granular after treatment.



FIG 210 Vitamin D resistant rickets. (Same patient as Fig. 201) Anteroposterior and lateral views of both legs (April 1954) Deformity in the leg bones is principally torsional. The left side also shows increased obliquity of the proximal tibial epiphysis. Some increased anterior bow is present in both tibiae. Widened demineralized metaphyses are present at both knees and ankles. On the lateral views of the ankles particularly on the left, can be seen bands of increased density which are indicative of abortive healing reaction.

hypercalcemia with levels above 12 mg per 100 cc. of serum.

A dose recommendation and reasonable regimen for outpatients is as follows³

300 000 I U of vitamin D daily with doses raised or lowered in relation to maintenance of the Sulkowitch test between + and ++. Some workers have indicated doses up to 1,000 000 I U daily to obtain healing.⁴

Thereafter the dose may be downgraded for maintenance. The level of maintenance is still determined by Sulkowitch test and still is many times the normal requirement.

Additional checks of blood-serum phosphorus should maintain the level between 2.5 to 3 mg. per 100 cc.⁶ If the phosphorus level rises above 4 mg. per 100 cc., hypercalcemia and hypercalcuria with clinical evidences of toxicity soon follow.

Anorexia, nausea and polyuria make it mandatory for the patient to report immediately for blood studies.

Radiographic checkups are important but it must be remembered that these lag several weeks behind biochemical evidences of osteoid calcification.

Vitamin D can be obtained in 50 000 I U capsules as Ertron (Whittier) and Drisdol[®] (Winthrop-Stearns) and in similar dosages by other leading firms. This condition is in the authors' opinion the only one in which enormous doses of vitamin D are indicated.

These patients do not have remissions and must take the indicated dose of vitamin D in controlled degree indefinitely. Their maintenance might be likened to that of a diabetic or Addisonian.

ORTHOPEDIC MANAGEMENT When a child

who receives a good diet and prophylactic vitamin supplements shows rachitic deformities this syndrome must be suspected. Proper blood urine and roentgenographic studies as indicated above should be done. Under the headings osteomalacia and rickets the broad group of deformities and their indicated treatment are delineated.

Orthopedic management in this group can follow a similar pattern. In the authors' opinion there is also no contraindication to surgery such as osteotomy. However great care to avoid complications following surgery is imperative in this syndrome. We must remember that immobilization of the total patient in bed or of parts of a patient in plaster or splints leads in itself to massive release of bone salts from the skeleton.

Since a patient with vitamin D resistant

rickets will first be placed upon a dose of vitamin D adequate to heal the lesions, he will be in a state bordering upon hypercalcemia.

When osteotomy and immobilization are done the extra release of calcium from the skeleton will probably throw the patient into a state of hypercalcemia, hyperphosphatemia and hypercalcuria. This could be severe enough to be serious.

It should be guarded against by reducing the calcium and vitamin D intake at the time of surgery and also by increasing the fluid intake. Furthermore, as early ambulation as possible should be encouraged. In some chosen instances in adults in particular there may be indication for intramedullary fixation.

Prognosis. There is no known cure. Control must be continued throughout life.

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Defects in Kidneys Affecting the Parathyroids and the Skeleton

(*Syn. Secondary hyperparathyroidism, renal osteitis fibrosa generalisata, renal rickets, osteomalacia*)

INTRODUCTION

Before discussing the present concepts of the relationship of kidney function to the parathyroid gland and to bone it would be well to review some of the older thoughts on this subject. It has long been known on a pathologic and a radiographic basis that bone changes of primary and secondary hyperparathyroidism are in many cases indistinguishable (compare Figs 119 to 131 with Figs 230 to 238). Pathologic sections in both types reveal evidences of osteoclasts, cysts and osteoclastomas.

Blood chemical studies reveal that in primary hyperparathyroidism blood calcium is elevated and blood phosphorus is lowered. In secondary hyperparathyroidism resulting from kidney disease there is an elevation of blood phosphorus concomitant with the nitrogen retention associated with the primary renal pathology. Blood calcium in these cases is lowered.

Renal disease responsible for this hyperphosphatemic hypocalcemic secondary hyperparathyroidism is usually a combined glomerular and tubular lesion (Figs 211 to 215). The phosphorus retention always has been clearly understood on the basis of diminished glomerular filtration. The lowering of the calcium was considered to be on the basis of the elevated phosphorus but recent studies indicate that there is a large component of hypercalciuria as a result of

tubular failure that is responsible for the hypocalcemia.

Many of these combined glomerular and tubular diseases are found in children with congenital renal anomalies or advanced chronic glomerular nephritis. The picture becomes confused by the influence of the disease state on the epiphyseal areas. Here wide osteoid seams and cupping similar to those of classical vitamin D deficient rickets are noted (Figs 216 to 220).

The osseous changes in these cases were termed renal rickets. This term has become part of medical nomenclature. It represents a condition in which renal glomerular and tubular disease, a so-called pannenephritis, produces a secondary hyperparathyroidism as a result of phosphorus retention. This excess parathyroid hormone produces bone changes which are clearly osteitis fibrosa generalisata with osteoclasts, cysts and osteoclastomas (Figs 230 to 238). In children however the epiphyseal zones show the widened osteoid bands and the metaphyseal cupping which led to the term renal rickets (Figs 216 to 220). Even adults will have widened osteoid seams around the bony trabeculae.

The secondary hyperparathyroidism on the basis of glomerular phosphate retention produces primarily bone changes commensurate with the diagnostic criteria of osteitis fibrosa cystica generalisata. There is, however, some tubular failure in these cases. Calcium is lost in the urine as fixed base to make up for the deficiency of ammonia production. A hypocalcemia will result. However the amineralization or the de-

mineralization of true rickets or its adult form, osteomalacia is not seen to any great degree. If it does occur it will be found usually at the epiphyseal zones of maximal growth. This is because even in the presence of the lowered serum calcium, the elevation of the phosphorus secondary to glomerular disease allows the solubility product to be above the critical level for osteoid calcification in most instances (Figs 221 to 222).

Actually, these concepts have been slow to evolve and even now are changing constantly. A major step in the understanding of the relationship between the bones, the parathyroids and the kidneys was the description of primary renal tubular disease. Here the glomeruli are normal. Now for the first time the tubular component of kidney disease, hypocalcemia with its manifestations of rickets or osteomalacia, can be studied independently (Figs. 223 to 229). In these cases the glomerular phosphate retention with its usual picture of renal osteitis fibrosa and marked secondary hypoparathyroidism is not present.

Two major types have been differentiated: the Fanconi and the Albright Butler groups. Tubular dysfunction with a loss of calcium is found in the Albright Butler group. In the Fanconi group there is combined loss of calcium and phosphorus because of renal tubular insufficiency. In the Albright Butler variety phosphorus is also lost in the urine as a result of increased parathyroid-hormone secretion secondary to the hypocalcemia. Even at this date the studies of the exact biochemical changes and the mechanisms of these various syndromes have not been completed fully. Their importance lies in the fact that for the first time a large group of



FIG. 211 Severe pancyphritis with secondary hyperparathyroidism and renal osteitis fibrosa generalisata. White female 34 years old. Roentgenogram of a postmortem specimen of the tongue and the neck organs. The shadows of the calcified larynx and the hyoid bone are evident. The lingual arteries are fully calcified. Metastatic calcification is also observed to outline three of the four hyperplastic parathyroid glands.



FIG. 212 Severe pannephritis with secondary hyperparathyroidism and renal osteitis fibrosa generalisata. (Same patient as Fig 211) Roentgenogram of the postmortem specimen of the heart shows widespread ectopic calcification involving the valves, the heart muscle and the coronary blood vascular tree.

kidney diseases which presented only tubular dysfunction with normal glomerular function have been delineated

In these diseases pathologic and radiographic findings are those of rickets in the young and osteomalacia in the adult (Figs. 223 to 229) Demineralization with lowered blood calcium and phosphorus and excess urinary excretion of calcium and phosphorus are present.

In both of these major groups of tubular kidney disease with increased loss of calcium and phosphorus in the urine there is

often an associated hypocalcemia. This hypocalcemia is not marked but does represent a mild stimulus toward secondary hyperparathyroidism. Some of these cases do appear to show some radiographic evidences of hyperparathyroidism such as loss of the lamina dura (Figs. 228 to 229). However histologic sections reveal principally wide osteoid borders of the trabeculae and no evidence of major osteoclasia or osteoclastoma or cyst formation.

The term renal rickets therefore becomes essentially a misnomer. The well known



FIG. 213 Severe pannephritis with secondary hyperparathyroidism and renal osteitis fibrosa generalisata. (Same patient as Fig. 211) Anteroposterior view of pelvis and lumbar spine. Note the severe generalized loss of bone substance. The process apparently has not been sufficiently long standing to produce cystlike osteoclastomas.



FIG. 214 Severe pannephritis with secondary hyperparathyroidism and renal osteitis fibrosa generalisata. (Same patient as Fig. 211) Chest plate. Observe the prominent lung markings and the numbers of dense lines, especially in the hilum. Much calcification of vessels was present in these areas at postmortem examination.

clinical entity of renal rickets long known to the medical world really represents essentially a secondary hyperparathyroidism with findings of osteitis fibrosa generalisata. The cupping and the epiphyseal changes seen in young subjects with this disease represent actually the tubular component of a pannephritis (Figs. 216 to 220). Loss of calcium in the urine as fixed base because of deficient ammonia production by the kidney prevents calcification of the osteoid at the epiphyseal areas. In the adult where no such osteoid proliferation is taking place at the epiphyseal plate only the findings of osteitis fibrosa generalisata could be noted (Figs. 211 to 215 and 230 to 238).

Only the newer pure tubular diseases produce findings essentially of demineralization—i.e., rickets or osteomalacia depending on the age of the subject (Figs. 223 to 229).

For purposes of classification on the basis of cause rather than effect, and to allow a clear program of treatment to be enunciated wherever possible it is the authors practice to divide kidney diseases as related to bone and the parathyroid glands as follows:

- 1 Glomerular disease with little or no tubular involvement. This is primarily an acute glomerulonephritis and usually will present little or no effect upon the bones or the parathyroid glands unless the disease goes on into group 3 as a pannephritis.

- 2 Tubular disease with little or no glomerular involvement. This is primarily an effect upon bones of calcium and phos-

phorus loss in the urine and consequent demineralization. The picture is primarily rachitic or osteomalacic (Figs 223 to 229). Parathyroid glands are involved only slightly on the basis of hypocalcemic stimulation.

3. The third group representing a pan-nephritis with mixed glomerular and tubular changes results in secondary hyperparathyroidism primarily on a hyperphosphatemic basis. In the growing subject the tubular lesion and the elevated serum phosphorus on the basis of retention may also produce enough hypocalcemia to prevent mineralization of the matrix. This, in the growing subject, will then produce rachitic manifesta-

tions at the epiphyseal junction (Figs 216 to 220). Although osteoid seams may be observed to be widened radiographically, and pathologically the primary lesion here is very definitely an *ostelitis fibrosa generalisata* (Figs 211 to 215, 221 to 222 and 230 to 238).

KIDNEY DISEASES AS RELATED TO BONE AND THE PARATHYROIDS

Diseases of the kidneys for purposes of effect upon the skeleton may be divided into 3 types: (1) glomerular disease with little



FIG 215 Severe pan-nephritis with secondary hyperparathyroidism and renal *ostelitis fibrosa generalisata*. (Same patient as Fig 211.) Anteroposterior, lateral and oblique views of forearm. There are fractures of both the radial and the ulnar shafts. Severe bone absorption is evident. This absorption is a combination of osteoclasia from glomerular disease and osteomalacia from tubular disease. In this particular example osteoclastoma reaction is not present. Note the similarity to findings of primary hyperparathyroidism shown in Figure 118.



FIG 217 Secondary hyperparathyroidism associated with renal disease producing renal osteitis fibrosa generalisata. (Same patient as Fig. 216) Anteroposterior view of pelvis. The bones are demineralized and are coarsely granular. The upper femoral metaphyses are sclerotic. The epiphyseal plates are somewhat broadened, although less so than in Figure 216. There may be great variation in the single case in the appearance of the various epiphyseal plates as regards the width of the osteoid zones and their degree of calcification.



FIG 218 Secondary hyperparathyroidism associated with renal disease producing renal osteitis fibrosa generalisata. (Same patient as Fig. 216) Anteroposterior view of both knees. Diffuse radiolucency and widened osteoid seams at the epiphyseal plates are present. These roentgenograms do not show the selective severe demineralization of the epiphyseal centers seen in infantile rickets. These cases require biochemical studies of the blood and the urine for full evaluation as the roentgenogram cannot distinguish the radiolucency of osteoclasts and the demineralization of osteomalacia.

reabsorption will not suffice and a hyperphosphatemia will result.

This disease therefore may cause a secondary hyperparathyroidism. Since the stimulus for increased parathyroid secretion is initiated by excess phosphorus in the serum, there may not be osteoclasts for the calcium-phosphorus product may remain above 30. (See Table 8 p. 468.)



FIG. 219 Secondary hyperparathyroidism associated with renal disease producing renal osteitis fibrosa generalisata. (Same patient as Fig. 216.) Anteroposterior view of both ankles. Widened osteoid areas at the distal tibial and the fibular epiphyseal plates are present. Associated trabecular coarsening of the rest of the bones is to be noted.



FIG. 220 Renal disease and secondary bone changes. (From Dr. M. M. Pomeranz.) Anteroposterior view of hand and wrist. The predilection of renal insufficiency to produce rachitic changes in the epiphyseal zones in children is shown here. The frayed metaphyses and the broadened uncalcified osteoid zones of the epiphyseal plates of the distal radius and ulna indicate the need for biochemical evaluation of the patient. There is little or no increase of radiolucency. Nevertheless the serum phosphorus was elevated indicating glomerular insufficiency. There was an associated lowered serum calcium possibly on the basis of an associated tubular lesion, but this also may be secondary to the elevated serum phosphorus. Such a roentgenogram cannot be considered diagnostic of the particular type of kidney disturbance affecting the bone. Compare with Figures 228 and 229 which show a Fanconi rickets of renal tubular origin only. Apparently the rachitic changes in growing bones are the result principally of the renal acidosis whatever its exact mechanism.



FIG 221 Renal osteitis fibrosa generalisata with secondary hyperparathyroidism. (Figs. 221 and 222 from Dr. M. M. Pomeranz.) Anteroposterior view of both hands. There are soft tissue calcifications bilaterally; the left hand and wrist being affected more markedly. Decalcification of the finger tufts is present in mild degree.



FIG 222 Renal osteitis fibrosa generalisata with secondary hyperparathyroidism. (Same patient as Fig. 221.) Anteroposterior view of right shoulder. Enormous soft tissue calcification is seen around the right shoulder joint area.



FIG. 223 Osteomalacia on the basis of renal acidosis (Albright Butler type) (Figs. 223 to 227 from Dr. Eugene P. Pendergrass) White female 46 years old. Chemical findings in this case included normal urea nitrogen diminished CO combining power low normal serum calcium definitely diminished serum phosphorus and markedly elevated serum alkaline phosphatase. The latter finding indicates unrequited osteoid tissue awaiting calcification. Renal disease is considered to be tubular in nature with loss of fixed base including calcium. Secondary hyperparathyroidism occurs as a result of the resulting hypocalcemia, and this in turn produces phosphorus diuresis and hypophosphatemia. Anteroposterior view of right shoulder girdle. (Prints are reversed.)

(Left) April 17 1941. A pseudofracture (Looser line) is seen at the base of the acromion process where it joins the main portion of the scapular spine. Such a line represents a zone of uncalcified osteoid. These cases have also been described as Milk man's syndrome following his early description of osteomalacia accompanied by pseudofracture lines on the roentgenogram. (Right) November 17 1941. The patient was given a high-protein high-calcium and high phosphorus diet with 10 000 units of vitamin D daily. The pseudofracture line of Looser in the scapular spine has filled in with calcification of the osteoid.

Hypocalcemia results because no osteoclasts occur with the calcium-phosphorus product above 30. The excess phosphorus in serum results in calcium phosphate formation and its excretion through the bowel.

No acidosis results because the tubules are conserving fixed base by adequate formation of ammonia. The urea clearance is diminished because of faulty glomerular filtration.

Treatment. Lower the phosphorus intake by diet. Such a diet reduces or eliminates milk meat cheese fish and eggs. Further reduce phosphorus absorption by administering calcium lactate and aluminum hydroxide (Dose: Aluminum hydroxide gel 50 cc. per day for average adult. Calcium lactate 12 Gm. per day.)

Prognosis. If kidney damage is not extensive or progressive the prognosis is good.



FIG. 224 Osteomalacia on the basis of renal acidosis (Albright Butler type) (Same patient as Fig 223) Today the authors prefer to use maintenance therapy of sodium and potassium citrate to provide fixed base in the extracellular fluid compartment for renal tubular excretion. This spares skeletal calcium and minimizes the danger of nephrocalcinosis and nephrolithiasis. The high-calcium high-phosphorus and vitamin-D intake is stopped after skeletal demineralization is corrected and pseudofractures have filled in. Anteroposterior view of left shoulder girdle. (Prints are reversed.) (Left) April 17 1941 There is a pseudofracture zone present at the base of the acromion process. (Right) November 17 1941 Following a calcifying regimen the zone of osteoid has calcified and is no longer visible in the roentgenograms.

TUBULAR DISEASE WITH LITTLE OR NO GLOMERULAR DISEASE (ALBRIGHT BUTLER VARIETY)

This phase of kidney disease results from loss of base economy with selective failure of calcium reabsorption.

The kidney tubules accomplish conservation of base economy in two ways by secretion of urine that is acid in relation to blood plasma and by elaboration of ammonia.

The ammonia combines with the excess acid radicals and thereby conserves fixed bases such as sodium, potassium, calcium and magnesium. When appreciable tubular disease is evident large amounts of fixed base combine with acid radicals and are lost in the urine. This depletes the body stores

of those bases. Acidosis with lowered serum CO_2 and a tendency to elevated serum chloride is present.

Calcium is the only element in sufficient supply so eventually it will be pulled from the blood.¹ As the serum-calcium level is reduced the parathyroid output is increased. This lowers the calcium and phosphorus product and osteoclasts results.

In addition increased phosphorus excretion through the urine results in a lowered serum phosphorus. Unless the tubular disease is very marked the stimulus to excess parathyroid secretion will not be as great as in total kidney disease with both glomerular and tubular involvement.

Actually this form may be helped by



FIG 225 Osteomalacia on the basis of renal acidosis (Albright Butler type) (Same patient as Fig. 223) Anteroposterior view of pelvis (Prints are reversed.) (Top) April 17 1941 Pseudofracture lines are present in both superior pubis rami with some seeming displacement on the right. Similar looser lines are seen at both ischiopubic junctions and in the femoral shafts at the level of the lesser trochanters bilaterally (Bottom) November 17 1941 Seven months after the institution of a calcifying regimen, complete healing of all pseudofracture areas has occurred.



FIG. 226 Osteomalacia on the basis of renal acidosis (Albright Butler type) (Same patient as Fig. 223) Lateral view of skull. A large decalcified area is seen at the top of the skull vault. Roentgenographically this resembles a zone of osteoporosis circumscripta in Paget's disease but is composed of uncalcified osteoid tissue.



FIG 227 Osteomalacia on the basis of renal acidosis (Albright Butler type) (Same patient as Fig. 223) Lateral view of lumbar spine. Osteomalacia has allowed biconcave compression of the body of the fourth lumbar vertebra by the expansion of the disk material into the softened bone.

providing extra base. This type of kidney disease favors nephrolithiasis and nephrocalcinosis because of the excess secretion of calcium and phosphorus in the urine.

Diagnosis. Symptoms may be anorexia, polyuria, polydipsia, renal calculi, weakness and lassitude. Vitiligo is often observed.



FIG 228 Rickets on the basis of renal tubular disturbance (Fanconi type) (From Dr M M Pomerans) Anteroposterior view of shoulder. A very wide band of uncalcified osteoid is present at the upper humeral epiphyseal plate. There is an associated displacement of the capital epiphysis into the varus position. The bones are markedly demineralized. Such a roentgenogram cannot be distinguished from glomerular renal bone changes. Compare with Figures 216 to 219



FIG 229 Rickets on the basis of renal tubular disturbance (Fanconi type) (From Dr M M Pomerans) Lateral view of ankle. A markedly broadened uncalcified epiphyseal plate is present in the distal tibia. The bones are so decalcified as to resemble a renal osteitis fibrosa generalisata. The differential diagnosis of these renal bone lesions with secondary hyperparathyroidism is on the basis of biochemical studies.

Deformities of the skeleton and fractures resulting from the osteoclasts may occur

X-ray Picture. This demonstrates osteomalacia or rickets depending upon the age of the subject. Looser lines (pseudofracture) may also be seen. These lines are multiple and symmetrical and occur in such places as upper femora, sides of pelvis, shoulder girdles and clavicles. These are actually not fractures but simply stress lines of osteoid that are uncalcified (Figs 223 to 227)

Urine. There is an increased urinary

calcium excretion and a fixed specific gravity at approximately 1.010 with a nearly neutral pH. There is a lowered total urinary ammonium and a lowered titratable acidity.

Treatment. This provides the use of alkali for the body to substitute for fixed base such as calcium. Such substances are sodium and potassium citrate and sodium bicarbonate.

Potassium is not good alone for it may produce undesirable cardiac effects. A very efficient regimen was advised originally by A. T. Shohl² to provide approximately 50 mEq of free base per 100 lbs of body



FIG 230 Renal osteitis fibrosa generalisata and secondary hyperparathyroidism. (Figs. 230 to 238 from the service of Dr. A. Bruce Gill, studied and followed by the senior author with chemical studies by Dr. E. P. Conson-White) White female, 20 years old. Chemical studies indicated some renal damage of combined glomerular and tubular types with azotemia and secondary anemia. Serum phosphorus was elevated with lowered serum calcium. Anteroposterior view of dorsolumbar spine and ribs. Note the marked loss of bone substance on the basis of osteoclasts. Deformities of the rib cage and scoliosis are severe. The ribs show widening and cystic changes. These roentgenographic findings are similar to those of primary hyperparathyroidism. Compare with Figures 119 to 131.

FIG. 231 Renal osteitis fibrosa generalisata and secondary hyperparathyroidism. (Same patient as Fig. 230) Lateral view of dorsolumbar spine. Severe osteoclasts is evident throughout. The sternum is widened, cystic and deformed.

Modification of this regimen as advocated by Talbot³ is as follows

Sodium citrate 58 Gm Potassium citrate, 62 Gm Water to 350 cc.	}	15 cc. of this mixture contains 25 mEq of calcium and phosphorus. 50 mEq of calcium and phosphorus are needed for each 100 lbs. of body weight per day in the average case. Divided doses are given with meals.
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weight per day. This mixture and method of administration are as follows

140 Gm. of citric acid 98 Gm. of sodium citrate	}	Dissolved in 1 liter of water (dose 50 to 100 cc. daily to amount necessary to overcome acidosis)
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Talbot's use of potassium with sodium citrate prevents further depletion of potassium and sodium.

Increased calcium and vitamin D intake helps to replace the calcium loss. Vitamin D is given in the therapeutic dosage of 10,000



FIG 232 Renal osteitis fibrosa generalisata and secondary hyperparathyroidism. (Same patient as Fig 230) Anteroposterior view of both humeri including shoulder joints. (Prints are reversed.) There is marked loss of bone density with expansion of the shafts and thinning of the cortices. Cystic changes are widespread. Step shadows are of ivory wedges used as a densitometer to grade the degree of bone absorption.

units daily until skeletal recalcification has occurred. Adequate calcium should be given in the form of milk, dairy products or calcium lactate or gluconate.

Prognosis. Healing of skeletal lesions will occur in a few weeks by x-ray check up. Calcium, phosphorus, CO_2 and chloride concentration in the blood will return to normal.³ Treatment must be continued as long as the disease is evident. When bones are fully recalcified, large doses of vitamin D and calcium are no longer necessary. Only maintenance levels are then required. Interrupted treatment may result in prompt relapse.

FANCONI SYNDROME⁴

This rare hereditary and sometimes familiar disorder results from disease of the

kidney tubules. These cases show no gross abnormality of serum glucose, amino acid or organic acid values. Yet, the urine contains excess amounts of amino acids, organic acids, glycogen and acetone. Obviously, since the serum levels of these materials are not abnormal, their excess concentration in the urine must infer a fault in tubular reabsorption of these substances.

Urinary calcium and phosphorus excretion are increased. Serum phosphorus is low. Serum calcium is normal or low. Serum CO_2 is lowered. The average urine pH is around 5.5. The titratable urinary acidity is thus increased.

Symptoms. (1) These patients show rickets by clinical and x-ray examination (Figs 228 to 229). (2) positive Sulkowitch



FIG 233 Renal osteitis fibrosa generalisata, and secondary hyperparathyroidism (Same patient as Fig. 230) Anteroposterior and lateral views of right forearm. Here there is loss of bone density and some cystic change but not to the degree observed elsewhere in this patient. The cystic change distinguishes this from an osteomalacia.



FIG 234 Renal osteitis fibrosa generalisata and secondary hyperparathyroidism (Same patient as Fig. 230) Anteroposterior and lateral views of left forearm. There is severe loss of bone density associated with osteoclasts from secondary hyperparathyroidism. Mild cystic changes are present. The healed malunited fractures were present when the patient was first observed.

test even though calcium and vitamin D are adequate (3) cataracts and congenital glaucoma and (4) mental retardation.

Treatment. Give base vitamin D and calcium similar to treatment outlined above for regular tubular disease.

TUBULAR DISEASE AFFECTING CALCIUM REABSORPTION (IDIOPATHIC HYPERCALCIURIA)

This condition is reported in adults. Most

cases are a result of kidney stone formation.¹ Base conservation is reported to be normal. The etiology is as yet undetermined.² Treatment as for the above two forms of tubular disease will be ineffectual.

Calcium and vitamin D would increase urinary calcium and increase the danger of

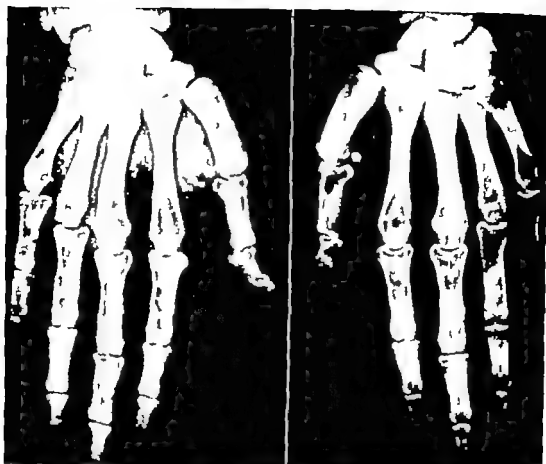


FIG 235 Renal osteitis fibrosa generalisata and secondary hyperparathyroidism. (Same patient as Fig 230.) Anteroposterior view of both hands. There is pronounced radiolucency from generalized osteoclasia. Cystic areas are present, especially in the proximal phalanges. The distal tufts are moderately demineralized.



FIG 236 Renal osteitis fibrosa generalisata and secondary hyperparathyroidism (Same patient as Fig. 230.) Anteroposterior view of pelvis and upper femora. (Print is reversed.) The bone structure here shows marked deformities and changes that are best observed rather than described. Both femora show malunited fractures. The bone structure is indistinguishable from that of advanced primary hyperparathyroidism (osteitis fibrosa cystica generalisata). Differentiation of these cases must be biochemical, not radiologic.

kidney stones. These cases have normal or low serum calcium and increased calcium excretion through urine.

The four metabolic disorders resulting in increased urinary calcium excretion are hyperparathyroidism, osteoporosis, renal tubular disease (Albright Butler or Fanconi)



FIG 237. Renal osteitis fibrosa generalisata and secondary hyperparathyroidism (Same patient as Fig. 230) Legs and knee joints. Anteroposterior view (Print is reversed) These structures show demineralization deformity of both tibiae and fibulae and cyst formation.



FIG 238. Renal osteitis fibrosa generalisata and secondary hyperparathyroidism (Same patient as Fig. 230) Lateral view of both feet. Severe osteoclasia and cyst formation are present. These cysts are of course osteoclastomas containing fibrous tissue which has filled in the areas of erosion in the bone

and idiopathic hypercalcaemia. It is the last form which Albright considers to be the most common.

MIXED NEPHRITIS WITH BOTH TUBULAR AND GLOMERULAR INVOLVEMENT

When reduction of glomerular filtration and tubular reabsorption occurs hyperphosphatemia and hypocalcemia result. On both counts this produces marked parathyroid stimulation hyperplasia and hypersecretion. There then results skeletal catabolism and a definite secondary hyperparathyroid state. Skeletal lesions in this condition are those

of renal osteitis fibrosa generalisata (Figs 211 to 215 and Figs. 230 to 238)

When such disease occurs systemic acidosis must result for there is no tubular adjustment. The resultant acidosis speeds skeletal catabolism through increased solubility of calcium and phosphorus and at the same time tends to prevent tetany through increasing ionized serum calcium. Yet the total serum calcium may be markedly lowered. In severe instances of hypocalcemia tetany may occur.

Glomerular disease is reflected in elevation of blood phosphorus and of N.P.N. and lowered urea clearance. Tubular involvement is reflected by fixed specific gravity of urine at 1.010 neutral pH and low urinary ammonium.

Treatment. This obviously involves a consideration of methods advocated for each single type—the glomerular and the tubular

1 Lower phosphates and acid metabolites by neutralizing with calcium lactate and aluminum hydroxide

2 Provide base such as sodium and potassium citrate to replace fixed base such as calcium. But care in piling up excess sodium and potassium must be maintained for alkalosis and edema are a danger

3 With calcium lactate vitamin D should

be given in order to promote absorption of calcium and to aid in combating the osteomalacia. Calcium lactate will combat acidosis, will provide further fixed base and also will combat tetany

If the kidney disease is not too severe, serum calcium and phosphorus levels will return to normal on this regimen. The bone lesions will heal and the acidosis will improve

Prognosis. The prognosis in this type of kidney disease, however, may be grave

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Defects in Matrix Formation

SCURVY

(Syn Vitamin-C deficiency scorbutus Barlow's disease Möller-Barlow's disease)

Definition. Scurvy is an acute or chronic deficiency disease due to a lack of adequate vitamin C or ascorbic acid. It is characterized by failure to maintain the intercellular substances of mesenchymal tissues in normal conditions. It is associated with various types of hemorrhagic manifestations, and in children with bone disorders as well as a disturbance of dentin formation (Figs 239 to 243)

Historical Notes. It appears that the word scurvy arose in the Middle Ages as a product of folklore but its clear etymologic origin is not known. It also appears that the word scorbutus was simply coined as a Latin-sounding variant of scurvy.

Early descriptions of this disease were related to voyages or explorations or campaigns that required distant travel for long periods of time without fresh foods particularly citrus fruits. The condition was known therefore, in the Crusades. Jacques de Vitry¹ described it as having occurred in the First Crusade in the thirteenth century. It was also described by Sire de Joinville to have occurred in the Seventh Crusade.¹

Then as voyages of exploration became more common during the fifteenth and the sixteenth centuries scurvy became more prevalent and a real hazard. It reached such proportions that Vasco da Gama lost 100 men out of a crew of 160 in a voyage around the Cape of Good Hope in 1497. In 1534 in his voyage up the Saint Lawrence River Jacques Cartier observed scurvy among his crew all but 10 of a crew of 110 being

afflicted by the disease. These people when they landed in Canada drank an infusion of the bark and the leaves of what appears to have been the spruce tree and materially improved from their affliction.²

References in the literature in early history were primarily those related to adult scurvy for in early times scurvy was not considered to be a disease of children. Whenever it was observed in children it usually was confused with rickets. Glisson,³ in 1650 in his famous treatise on rickets made the first differentiation between rickets and scurvy but his description apparently was overlooked for more than 200 years.

In 1753 James Lind⁴ a physician who formerly had been a naval medical apprentice for 9 years published his observations and recommended the use of lemon juice for the prevention and the treatment of this disease. He made every effort to have the British Navy adopt the use of lemon juice during his lifetime but it was not until a year after his death, and 41 years following the publication of his treatise that lemon juice was added to the rations of British sailors with the result that scurvy disappeared from the British navy. The British navy man of course had been referred to for many years as a "limey" or a "lime juicer." It appears that prior to the routine use of lemon juice in the rations of British sailors lime juice was considered to be an agent that protected against the development of scurvy. This material was more expensive but not so high in ascorbic acid content as lemon juice. It is of interest that numbers of suppliers of the Navy when they had supplied pure lime juice were prosecuted under the assumption that they



FIG 239 Scurvy Lateral view of lower extremities. Wimberger's lines show about the distal femoral and the proximal tibial epiphyses. Fraenkel's line and Pelkan's spurs are to be seen, particularly at both lower tibial and femoral metaphyses. Mild periosteal separation and calcification are observed about the left femur. All the bones present a ground-glass osteoporotic appearance.



FIG 240 Scurvy Lateral view of knee joint. Wimberger's circle outlines the distal femoral and the proximal tibial epiphyses. Fraenkel's line and Pelkan's spurs are to be seen at the distal femur. Periosteal reaction is present about the lower femur.

had provided diluted material because the men developed scurvy upon it, whereas individuals who had mixed their lime juice with the cheaper lemon juice had actually diluted it, thereby making a cheaper variety. But they were not prosecuted since the greater concentration of ascorbic acid in the lemon was a protection against scurvy. Presumably in this instance, honesty was not the best policy.¹

Since the early 1800's although the precise nature of the disease was not understood fully, an effective method of prevention and treatment of the condition was known so that adult scurvy became practically nonexistent except in times of famine and war. Infantile scurvy, as indicated above, was

recognized by Glisson and differentiated by him from rickets. Yet confusion continued, with scurvy and rickets being considered the same. Möller as late as 1800² described scurvy as an acute rickets and overlooked its separate identity. This greatly confused the issue, especially in Germany where they did not differentiate these diseases until after the English had done so.

Cheadle³ in 1878 differentiated scurvy from rickets in infants and in 1883 Barlow wrote a classic paper⁴ in which he clearly defined this disease. He also understood its treatment.

The hesitancy or the confusion in making this differentiation from rickets came about because no one could believe that this disease which had been observed for centuries in adults could possibly affect children. It is also quite reasonable to assume that differentiation may have been difficult because of the possibility that if patients were deficient

in one vitamin they were deficient in others and that rickets and scurvy occurred simultaneously on frequent occasions.

The first experimental production of scurvy in animals was in 1907 by Holst and Frölich,⁸ whose work paved the way for study of the vitamin as it occurred in nature. The next step in this picture was that of Szent-Györgyi,⁹ who isolated a crystalline substance from the suprarenal glands of oxen and from various plant sources. He proved this crystalline compound had the formula $C_6H_8O_6$ and named it hexuronic acid; this of course was the first isolation of ascorbic acid. It was not until 1932 that he fully demonstrated its vitamin characteristics in his animal feeding experiments.¹⁰

Further corroboration of the effectiveness of this compound was reported upon by Waugh and King.¹¹ Since this time scurvy has presented no problem to the informed physician. Its clinical characteristics are

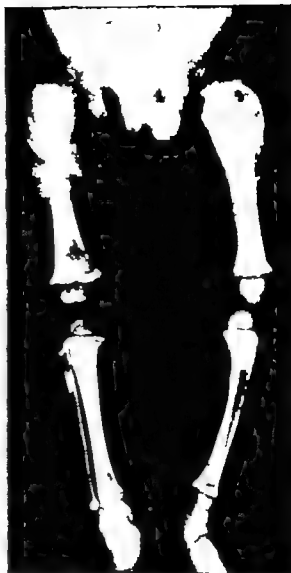


FIG. 241 Scurvy. Anteroposterior view of lower extremities. Wimberger's circle and Fraenkel's line are well denoted. In the lower femora Pelkan's radiolucent scurvy lines are observed. Both upper femora, in particular, show periosteal proliferation which is more marked on the left. All the bones show increased radiolucency.



FIG. 242 Scurvy. Anteroposterior view of upper extremity. Marked ground-glass appearance of the humerus due to osteoporosis is evident with an organized healing reaction of subperiosteal hemorrhage.



FIG 243 Scurvy (Same patient as Fig. 242 following antiscorbutic therapy) Anteroposterior view of upper extremity. Proliferative periosteal reaction is being incorporated into the humeral shaft. The osteoporosis has disappeared and the bones are of normal texture.

well known and its chemical findings are definite and can be identified.

Etiology. Either total lack or deficiency of vitamin C for a long period of time is the cause of scurvy. This condition may result from food idiosyncrasies or from an inability to eat those foods high in this material. It may occur in gastro-intestinal disease when the patient is on a diet chiefly of milk, cream, cereals, and eggs, as for ulcer.

The pathologic physiology of this condition can be well interpreted in light of the data of vitamin C as reported in Part One. It is important to remember that this vitamin is water-soluble and heat labile, cannot be synthesized by the human organism and is not stored in the human. The average requirement is 1 mg. per kg. of body weight per day (see Table p. 78).

Clinical Characteristics. In infants scurvy is more apt to occur between the sixth and the twelfth months. The symptoms are poor appetite, inability to gain weight and irritability. Many times when the child is touched (particularly over the tibial crest, for instance) he may scream with pain. Often he will fail to move one or both legs or arms, the reason therefor being tenderness over the bones from subperiosteal hemorrhage and not from a paralysis as often is assumed (Figs. 242 to 243).

Hemorrhagic findings include skin petechiae and bleeding spongy gums. When there is a severe vitamin-C deficiency the costochondral junctions of the ribs may be enlarged. It is true that the enlargement is angular rather than rounded as in rickets, yet swelling of the ends of the long bones, especially over the lower femur and the upper tibia, also occurs. One easily can see that these things could lead to a diagnosis of rickets especially before the days of the roentgenogram.

The disease in infants and children may and often does progress to such a degree that the epiphyses become separated from the shaft of the long bone. This is observed by the bayonet deformity of the ribs where the costal cartilages separate from the ribs and depress with the sternum. Change of this type can and does occur in the long bones.

Adult scurvy is much slower in development than the childhood form—as a matter of fact the time required may be from 3 months to 1 year for severe scurvy to develop.

Were infection to develop during the time that the patient is on inadequate vitamin C, the extra metabolic stress would hasten the appearance of scurvy and would make the attack more intense.

The adult symptoms are irritability, general aches and pains, weight loss, weakness, lassitude, bleeding gums of spongy type, gingivitis, and loosening of the teeth. Hemorrhagic manifestations are purpura with petechiae and massive hemorrhages into muscles and subperiosteally. The skin

will bruise from even slight pressure and large hemorrhages may occur into the muscles so there are, in short large swellings involving the muscles and purpuric skin reactions.

When a tourniquet is placed around the arm (the capillary fragility or Rumpel-Leede test) petechiae occur on the forearm as the small capillaries rupture. Late in the disease nosebleeds bleeding from the eyes bleeding into the brain and gastro-intestinal and genito-urinary bleeding will occur. The primary bone lesions that occur are associated with hemorrhages under the periosteum associated with trauma, but bone lesions are mild and rare in the adult. In the adult, also great tendencies for transudates develop i.e. edema fluid forms in pleural and peritoneal cavities without any contamination by blood.

Pathology Scurvy is associated with disturbances of the normal development of intercellular substances of tissues derived from the mesenchyme. The capillary walls are weakened and subject to hemorrhage. Wounds heal poorly in this condition.

Considerable changes occur in bone particularly in children (Figs 239 to 243). In the adult, except for periosteal hemorrhages bone changes are essentially unimportant. In children endochondral bone growth may cease due to failure of osteoblasts to form osteoid tissue. Cartilage becomes calcified but is not properly absorbed and replaced by osteoid.

In children epiphyseal lines become irregular and widened. There is often dislocation of the epiphysis with displacement of the cartilaginous portion.

The costal cartilages at the junctions of cartilage and bone may sheer off. The cartilages slide backward with the sternum so that a so-called "bayonet deformity" develops. This is angular in contrast with the enlargement associated with rickets which is rounded.

The tendency for hemorrhage beginning at the epiphyseal area often results in small calcified spurs being observed just at the sides of the epiphyseal plates. The zone of

provisional calcification becomes broadened and irregular and the cartilage becomes calcified and forms a so-called white line of Fraenkel¹² (Figs 239 to 242). The defect is that the osteoblasts are not normally active and they do not invade in a normal fashion and the capillary loops do not form normally. Therefore the substitution of bone matrix for cartilage as occurs in normal endochondral bone formation does not progress.

The periosteum becomes elevated by large amounts of hemorrhagic effusion. Large amounts of calcification of cartilaginous components may be observed at the epiphyseal edges so that the ends of the bones become thickened also. In healing a very wide degree of calcification will rapidly be observed throughout this hemorrhagic area. The epiphyseal center itself is clearly identified by a circling zone of calcification known as Wimberger's line¹³ (Figs. 239 to 242). This represents endochondral cartilage that is calcified but not properly invaded by osteoblastic tissue.

ROENTGENOLOGIC FINDINGS. To follow changes from the epiphyseal center into the center of the shaft we have the Wimberger's circle¹³ which is a thin calcified line that outlines the epiphyseal center. Next at the shaft side of the epiphyseal plate is a dense calcified line. This is Fraenkel's white line¹² or the "Trummerfeld zone." This is a phenomenon similar to Wimberger's line and represents calcification of cartilaginous component not properly invaded by osteoblasts and capillary loops. At the lateral and the medial edges of this line a small bonelike spur is observed. This is referred to as Pelkan's spur¹⁴ (Figs 239 to 242).

As we progress farther down the shaft just past this white line and the spur into the metaphysis we reach a translucent zone of metaphyseal rarefaction which is referred to as the scurvy line of Pelkan¹⁴ or the "Gerüstmark" of Schödel and Nauwerck. This area is an area of disorganization in normal bone development. Here are found the poorly defined capillary loops with hemorrhage and deficiency of osteoblasts or



FIG 244 Congenital syphilis Anteroposterior view of trunk and upper extremities. There are a bilateral and a symmetrical metaphysitis and a periostitis of the bones of the upper extremities. It differs from scurvy in that there is no osteoporosis. There is no evidence of Pelkan's spur Wimberger's circle or the dense line of Fraenkel in any area Contrast with Figures 239 to 243

osteoblastic activity with no new bone formation and for that reason it is radiolucent. It is in this area of translucence that the bones give way with microfractures and even the separation of the epiphysis from the shaft (Figs 239 to 242)

The next major finding is the washing out of bone substance throughout the shaft, or the so-called ground-glass appearance (Figs. 239 to 242) Finally the separation of the periosteum will not be shown necessarily on the radiographic shadow during the active stage of the disease. However where healing occurs very rapid calcifica-

tion can be seen subperiosteally (Figs. 239 to 243) The general cortical outlines are also thinned

X ray changes are summed up by the following findings

- 1 Wimberger's circle (calcified line outlining epiphyseal center)
- 2 Fraenkel's line or Trummerfeld zone (dense calcified line marking end of metaphysis)
- 3 Pelkan's spur (small bonelike spur on either side of Fraenkel's line)
- 4 Pelkan's scurvy line (translucent zone of metaphyseal rarefaction)
- 5 Ground-glass appearance of entire shaft and epiphyses
- 6 Subperiosteal calcification with separation of periosteum.

LABORATORY FINDINGS The reader is referred to the section on vitamin C in which this problem is discussed in detail.

A confusion factor in careful laboratory determination is the consideration that tissue saturation of vitamin C occurs. This tissue saturation which is normally present when adequate vitamin C is taken in must be practically completely depleted before any change occurs in the blood levels, or before appreciable change in vitamin-C excretion in the urine is found to occur

Blood levels therefore, run from 0.5 to 2.5 mg per 100 cc. and average about 1 mg per 100 cc. If figures are below 0.5 mg one may be suspicious of scurvy The white-cell centrifuge method with determination of vitamin-C content in the white-cell platelet material is presumed to be a more diagnostic method This ranges from 6 to 58 mg per 100 Gm. of leukocytes or platelets. Obviously levels below 6 would be subject to consideration of scurvy

Urinary excretion depends upon whether tissue desaturation has occurred If a scorbutic situation occurs and a large dose of vitamin C is given practically none of it will be excreted in the urine and this of course would be a key method of diagnosis and could be considered as a vitamin-C



FIG 245 Congenital syphilis. Lateral view of both lower extremities. A bilaterally symmetrical periostitis affects all the long bones. The rarefying metaphysis has none of the diagnostic criteria observed in scurvy. Contrast with Figures 239 to 243. Clinically, congenital syphilis usually presents in the first few weeks of life; scurvy is rarely present in the first 6 months of life.

tolerance test. An individual whose tissues were saturated would be expected to excrete through the urine almost any excess intake of vitamin C. Apparently, 1 mg. of ascorbic acid per kg. per day appears to be the maintenance dose. Any excess above this would be the amount excreted by such a normal control.

Prophylaxis. For prophylaxis a diet adequate in vitamin C, either by food such as orange juice or lemon juice, tomato juice or by synthetics such as ascorbic acid, will suffice. Adequate amounts are considered to be 1 teaspoonful of orange juice daily from the second to the fourth weeks of life, increasing in amount until at about 5 to 6 months of age the intake is 2 to 3 ounces. Tomato juice requires at least three times that amount. If the infant cannot tolerate vitamin C in this food fashion, then intake levels should be 1.5 to 2 mg. of ascorbic acid

per kg. If ascorbic acid is used, this is the method of measurement. Of the amount required, there appears to be no toxicity from excess amounts, so there is no harm in giving more of ascorbic acid. The reader is referred to the section on vitamin C in Part One, where the maintenance requirements of the vitamin are covered for all age groups (see Table p. 78).

Differential Diagnosis. Infantile scurvy may be differentiated from blood dyscrasias or allergic purpuras, rheumatic fever, and poliomyelitis. Rickets occurs at an earlier period of life than scurvy. Scurvy rarely occurs before the sixth month. No hemorrhagic manifestations are present in rickets. In rickets, the swellings, for instance of the costochondral junction, are rounded, whereas those in scurvy are angular. Roentgenograms are quite diagnostic. In the first half year of life, though the disease must be

differentiated from congenital syphilis with primary metaphysitis and from infantile cortical hyperostosis of Caffey (Figs 244 to 245 and Figs 327 to 330)

Treatment. When true scurvy is present very large doses of ascorbic acid are required. In infants a minimum of 300 mg daily is required. Dosages of this type can be carried out for at least a month and by that time the usual prophylactic dose will be adequate because saturation of tissues will have occurred.

In regard to individuals who are unable to

take the vitamin C by mouth, it has been recommended that intravenous preparations of 500 to 1 000 mg can be given daily. In adults, as a matter of fact, it is considered that up to 1 000 mg of ascorbic acid daily for at least a week or more is required in order to saturate tissues.

Prognosis. The prognosis may vary from varying degrees of disability to death. This however is a very unlikely occurrence in modern life. In the Western world in particular treatment may be expected to produce a cure.

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Hypervitaminoses

HYPERVITAMINOSIS A

For many years it has been known by Arctic explorers that the liver of polar bears is poisonous. This is now understood to be the result of hypervitaminosis A for the liver of these bears is enormously rich in this substance containing approximately 20 000 IU per Gm.

More recently with the advent of concentrated vitamins hypervitaminosis A has been reported particularly in infants and in children. So often an enthusiastic parent believes that an extra dose is that much better. It is also therefore just as important to learn whether a child is getting too many vitamins as well as whether he is getting too few. Hypervitaminosis A will occur if the average dose is more than 100,000 IU per day.

Symptoms and signs¹ are

- 1 Sparse coarse hair
- 2 Disappearance of the eyebrows
- 3 Dry rough skin
- 4 Hemorrhagic diathesis including subperiosteal hemorrhage
- 5 Hepatomegaly without splenomegaly
- 6 Fragmented epiphyses
- 7 Decalcification.
- 8 Expansion of bone—especially the shafts of long bone. It appears to be a subperiosteal proliferative reaction (Fig. 246).
- Painful swollen extremities
- 9 Carotinemia with a yellow discoloration of the skin
- 10 Increased vitamin A in blood² levels over 300 IU per cc.

11 Signs of liver damage (a) hyperprothrombinemia related to hemorrhagic diathesis (b) elevation of alkaline phosphatase and (c) increased serum lipid.

Differential Diagnosis. This condition

causes bone changes similar to those of infantile cortical hyperostosis³ and congenital syphilis (Figs. 244 to 245). In addition it must be differentiated from other diseases which cause liver enlargement and hemorrhagic phenomena. The hemorrhagic effects of scurvy and the painful swellings from subperiosteal hemorrhage in this condition are a case in point (Figs. 239 to 243).

The chemistry showing elevation of blood vitamin A, history of excessive administration of vitamin A and no fever or leukocytosis differentiates the condition from infantile cortical hyperostosis (Figs. 327 to 330).

Scurvy will be identified by other signs: gums bleeding, growth disturbances, low vitamin C and rapid healing on administration of vitamin C which is not toxic in any amount.

Congenital syphilis will show radiographic evidence of metaphysitis (so-called luetic osteochondritis) as well as periostitis (Figs. 244 to 245). Furthermore serology is significant.

Treatment. Stop vitamin A. Give vitamin K if there is elevated prothrombin time with hemorrhagic signs.

Prognosis. Excellent and full resolution usually will occur. This includes reabsorption of the periostitis and return of the bone structure to normal.

HYPERVITAMINOSIS D

There has been much discussion about whether or not there may be different forms and actions of vitamin D. For practical purposes it is not necessary to look for varying actions of different fractions.

The authors previously have discussed (In Part One) the physiology of vitamin D.

The problem now is in relation to under-
standing hypervitaminosis D. Within the
past 15 to 18 years there has been much
enthusiasm for vitamin D administration in
enormous doses for the treatment of rheu-
matoid arthritis in particular.

Many reports following the original one
of Dreyer and Reed¹ were encouraging, and
its use increased. One wonders whether the
steroid vitamin D may have represented a
rich source of raw material for cortisone
manufacture. In any event, as expected by
many who had experience with this sub-
stance, severe toxic reactions to enormous
doses occurred.

Work on hypervitaminosis D goes as far
back at least as 1929.² In 1930³ study on
rats also showed untoward effects from large

doses of vitamin D. The effect was the same
whether parathyroids were present or ab-
sent. Such toxic effects easily were found to
be related to those of dihydrotachysterol.
This is obvious because dihydrotachysterol
is only slightly less active than vitamin D
in promoting calcium absorption from the
intestine. Within the past 10 years, many
people have received enormous dosages
of vitamin D—up to 150,000 units per
day and more. From this group numbers
of cases of hypervitaminosis D were re-
ported upon.

The *modus operandi* of vitamin D in very
large doses is twofold. The first results from
the action of vitamin D in increasing cal-
cium absorption from the gut. The sequence
of events is as follows:

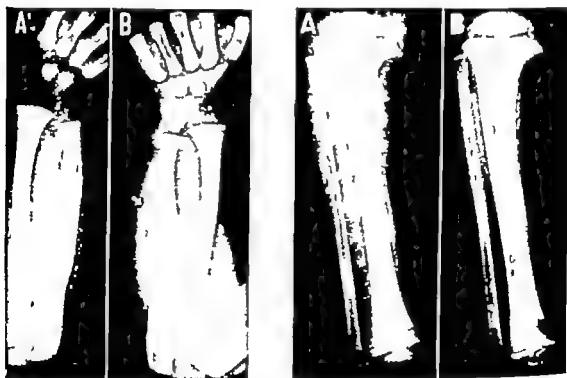


FIG. 246 Hypervitaminosis A. (From Dr. John Caffey and reproduced with permis-
sion from *Pediatric X-ray Diagnosis*, ed. 2, p. 748, Chicago Yearbook, 1950.)
White female, 21 months old. The patient had received 1 teaspoonful of oleum per
codonophum daily for 9 months. Anteroposterior views of forearms and leg. Roent-
genograms of both ulnas (A and B) were taken 5 weeks after onset and show bilateral
symmetrical cortical hyperostoses as a result of vitamin-A poisoning. Tibia (A)
5 weeks after onset shows cortical hyperostosis and spur on the medial aspect of the
proximal end of the tibial shaft. (B) 10 weeks after onset and 5 weeks after stopping
vitamin A shows increased mineralization and incorporation of the periosteal reaction
into the tibial shaft.

- 1 Increased calcium absorption from the intestinal tract
- 2 Hypercalcemia.
- 3 Depression of parathyroid activity
- 4 Decrease in urinary phosphorus excretion
- 5 Hyperphosphatemia
- 6 Excess calcium phosphate in the serum with deposition of this compound in soft tissues throughout the body

The second action of vitamin D in enormous doses is a direct effect on the renal tubules, where its action resembles that of parathyroid hormone. Here there results a phosphorus diuresis with a tendency to hypophosphatemia and hypercalcemia.

Actually, these two separate mechanisms of vitamin D action are somewhat antagonistic as regards serum and urinary phosphorus levels. It appears in general that the first action predominates if calcium intake is normal so that hypercalcemia is generally reinforced by hyperphosphatemia. The tendency toward metastatic calcification is thus increased.

Symptoms of this condition are of three types

1 Those resulting from hypercalcemia (a) anorexia (b) nausea, (c) vomiting (d) diarrhea (e) abdominal pain (f) lethargy and (g) general muscle weakness which if severe enough may even be associated with constipation.

2 Renal symptoms. The cause is calcification of kidney substance. Probably it occurs within the glomeruli, the tubules and the renal pelvis as well as in the interstitial structures. Symptoms and signs would in-

clude (a) albuminuria (b) hematuria (c) azotemia (nitrogen retention), (d) polyuria and (e) polydipsia

3 Symptoms and signs associated with metastatic calcification of any or all soft tissues or organs. Blood vessels, kidneys, heart, lungs, gastric mucosa—all may show this and cause symptoms related to disturbance of their respective functions.

Vitamin-D toxicity. If continued long enough without severe kidney damage may eventually cause negative balance of calcium and phosphorus and production of osteomalacia⁴ of bone. To produce such an effect the mechanism may occur from two points of view: (1) the stimulation of excess parathyroid secretion by hypercalcemia and hypercalciuria. This is associated with the decrease of phosphorus excretion via the kidneys and a secondary hyperphosphatemia. (2) Another effect of vitamin D, namely a parathyroid hormone-like action of vitamin D causes phosphorus diuresis.⁵ It is not a likely or a common reaction because the kidneys are affected with such frequency.

Treatment. (1) Reduce vitamin D intake (2) Reduce calcium intake (3) Force fluids.

Prognosis. This is dependent upon the degree of renal damage and metastatic calcification. If the condition has been identified early, recovery will occur. If the changes are severe, even death may ensue.

Except in vitamin D resistant rickets, it is questionable whether large doses of vitamin D should be used at all. When used, careful check-up of blood and urinary calcium is essential.

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Lipoid Granulomas

EOSINOPHILIC GRANULOMA

(Syn Myeloma with presence of eosinophils granulations tumor osteomyelitis with eosinophil reaction solitary granuloma of bone)

Definition. Eosinophilic granuloma is an inflammatory reaction involving the reticulo-endothelial structures of bone and is characterized by collections of variegated cells ranging from histiocytes to eosinophils. Although it was described originally as a solitary lesion of bone more recently it has been found to be multiple in bone and even to occur in soft tissue in association with bone lesions (Figs 247 to 252).

Historical Notes. Schafer¹ reported a case of osteomyelitis in the skull with a histologic reaction of eosinophils in 1938. Lesions had previously been described which later were thought possibly to be eosinophilic granuloma but these references did not define this particular condition clearly and in general were overlooked. Among these references are the following:

Finzi in 1929 described a case of myeloma with eosinophils in the frontal bone in a patient of 15 years.²

Mignon described a "granulations tumor" of the skull.³

Recent pathologic studies of a more definitive type began with the work of Otani and Ehrlich in 1940.⁴ They described a solitary granuloma of bone. Lichtenstein and Jaffe⁵ described this condition as eosinophilic granuloma of bone.

Green and Farber⁶ reported 10 cases of this lesion in 1942 and their conclusion may be quoted as follows:

These benign destructive lesions of bone do not constitute a new disease but represent rather one variant of a basic disease process

of which the clinical pictures known as Hand-Schüller-Christian disease, certain forms of xanthoma, and Letterer-Siwe disease are other examples.

Incidence. The disease occurs primarily among older children, adolescents and young adults. Males are affected more commonly than females. According to Fairbank⁷ the proportion is 5 to 1.

Etiology. The cause is unknown. Cultures have been taken; they are negative.

Clinical Features: PHYSICAL SIGNS AND SYMPTOMS. The lesion may be silent and evident only upon an incidental roentgenogram. On the other hand it may give rise to local pain, swelling and tenderness. The local lesion may be fluctuant and there may be general symptoms such as malaise and elevation of temperature. Sometimes there may be a pathologic fracture if the lesion is extensive enough. When it involves the skull an actual depression can be felt at the site of involvement.

Headache may occur in cases in which there is involvement of the skull.

The lesion involves bone primarily and actual destruction of bone can and does occur. Furthermore this lesion can break through the cortex of bone and through the overlying soft tissue to erupt upon the surface with the formation of a fistulous tract. This tract will then show a skin granuloma.⁸

Dermatologists have reported a papular erythematous skin lesion.⁹

The question of visceral involvement and its possible relationship to Hand-Schüller-Christian and Letterer-Siwe diseases has been discussed further by Mallory,¹⁰ who highlights the importance of the histiocyte in both eosinophilic granuloma and Letterer-Siwe disease. Letterer-Siwe disease occurs



FIG 247 Eosinophilic granuloma. (From Dr M M Pomeranz) White female 10 years old. A large osteolytic area without surrounding reaction is present in the proximal metaphysis of the femur.

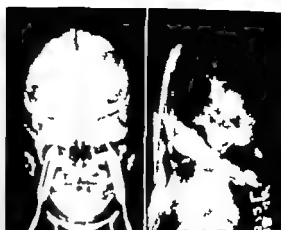


FIG 248 Eosinophilic granuloma. (From Dr M M Pomeranz) Antero-posterior and lateral views of skull. There are multiple zones of bone destruction throughout the calvaria. The lesions are roughly circular and have in general a halo of further erosion around them.

the age of onset—the earlier the involvement as a rule the more serious the problem (3) that milder manifestations may represent certain healing situations as in the possible lipoidification of the histiocytic lesion in Hand-Schüller-Christian disease. It is rather interesting that diabetes insipidus¹¹ and infiltration of lung fields¹² have been described in eosinophilic granuloma, as well as in Hand-Schüller-Christian disease.

LOCALIZATION The lesions may be found widespread throughout the skeleton. They are more common in the axial skeleton, including the skull but the limbs are involved also (Figs 247 to 252).

CHEMISTRY No gross blood-chemistry changes are observed in this condition. However the blood count may show moderate leukocytosis at times associated with relative eosinophilia.

X-RAY FINDINGS The lesions are definitely bone-destructive or lytic lesions and there may be some periosteal new bone formation particularly when the lesion is close to the subperiosteal area (Figs. 249, 250 and 251). As indicated above the involvement is of the axial skeleton including the skull and the proximal extremities, pri-

in much younger individuals as a rule and is primarily visceral and uniformly rapidly fatal. Hand-Schüller-Christian disease is a much slower process occurring in adults and children and may represent collagenization and lipoidification of the histiocytic lesion. This is possibly the same sort of condition because some of these cases especially where there is damage to vital organs go on to fatal termination as in Letterer-Siwe disease. In all therefore much argument can be presented to indicate that all three have much similarity. They differ on the basis (1) of severity with particular attention to visceral involvement (2) of

marily above the elbows and the knees as well as the ribs (Figs. 247, 248 and 252). Other areas however (even on the lower portions of extremities even involving the fingers) have been observed and noted.

The most common area affected is the skull primarily involving any portion of the calvaria. The lesion is sufficiently destructive so that pathologic fractures are common and once fracture occurs healing is promoted as a reaction to the fracture.

Although originally many cases were considered to be solitary careful skeletal survey after finding one lesion often has disclosed lesions involving other portions of the skeleton. One must, of course bear in mind that there may be associated changes and involvement of soft tissue as well as of bone.

At times one lesion may occur and heal and then other lesions will appear elsewhere in the skeleton and heal and still others appear somewhere else again—somewhat of a chain reaction.

Pathology: Gross Appearance. These lesions are destructive in type and are roughly round or oval. The area destroyed by the lesion is replaced by soft tissue. This soft tissue varies in composition depending upon the stage of the lesion whether early or late. In the early lesion, this tissue is quite soft and brown but it is not necrotic and therefore not friable. Later the lesion becomes fibrous and grayish in color. Hemorrhage may occur in these lesions as degeneration of the lesion progresses or when fracture occurs it will show as gross

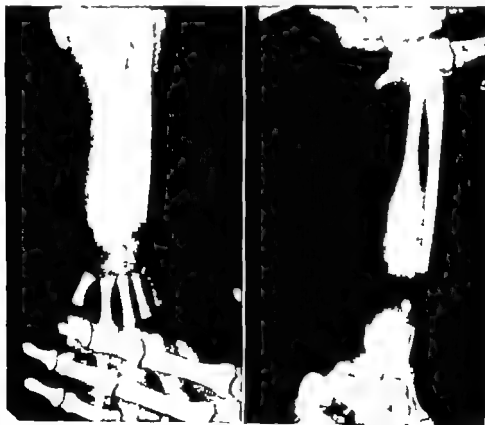


FIG. 249 Eosinophilic granuloma. (From Dr. M. M. Pomeranz.) Anteroposterior and oblique views of forearm. This is a very large lesion involving the distal half of the radius with destruction of the medial cortex. There are periosteal elevation and new bone formation at the junction of the involved and uninvolved portions of the radial shaft. There is some reparative reaction giving rise to the multiloculated appearance.

evidence of blood extravasation. Necrosis of the lesion may also occur and then the tissue will be found to be quite friable.

The lesion is purely destructive but may produce new bone formation. Moreover, when fracture occurs, there is proliferative reaction to the fracture with new bone formation.

MICROSCOPIC APPEARANCE. Pathologists agree that the primary pathologic cell is the histiocyte which shows as sheath like collections. These cells may contain either droplets of neutral fat or disintegrated cellular material. These histiocytes coalesce to become multinucleated giant cells. This is particularly noticeable when there has been hemorrhage and/or necrosis for they then pick up the debris of eosinophils, red blood cells and other cellular breakdown material.

The early lesions contain large numbers of focal collections of eosinophils, and it is this finding which apparently is a secondary reaction which resulted in the term eosinophilic granuloma.

The histiocyte the primary cell of this process appears to be derived from the reticulum cell of the marrow. With maturation of this lesion fibrosis (and sometimes xanthomatosis if there is a lipid infiltration of the histiocyte) occurs. This picture then approximates that of Hand-Schüller-Christian disease particularly since in the older lesion the eosinophils disappear.

A differing point of view however is presented by Jaffe and Lichtenstein¹² who state that this lesion may heal spontaneously by resolution and does not have to go through a stage of lipid infiltration.

Treatment. Curettage is curative. x-ray therapy is very effective. After curettage it is not necessary to put in bone chips although one may do so if he so desires. Following roentgen therapy, the lesions fill in and appear to heal beautifully.

Prognosis. Prognosis is good in the majority of cases. This infers the benign type of solitary or multiple involvement. However as has been indicated this may overlap



FIG. 250 Eosinophilic granuloma (Figs. 250 and 251 from Dr. M. M. Pomeranz). White female 11 years old. Anteroposterior view of lower ribs. There are expansile lesions in the right ninth and eleventh ribs. Periosteal lifting and reaction have occurred. Bone formative response is seen in the involved areas. An osteolytic central zone is present in the ninth rib.

to assume characteristics of the more serious reticulo-endothelial affections such as Letterer Siwe and Hand Schüller-Christian diseases. In these instances the prognosis would be related to the severity of the disorder and the extent of visceral involvement.

LETTERER SIWE DISEASE

(Syn Reticuloendotheliosis nonlipoid reticuloendotheliosis nonlipoid histiocytosis.)

History Apparently this syndrome or disease entity was not identified until Letterer¹ described it in 1924. It was subsequently

reported upon by Siwe² in 1933. Letterer reviewed the subject in 1934.³

Incidence. It is a disease of infants rare after the age of 2 or 3. There are not many cases reported. Both sexes may be affected. It is regarded by some as an acute form of Hand Schüller-Christian disease.

Etiology The etiology is unknown, although some have postulated an infectious background because of its acute course terminating fatally.

Clinical Features: PHYSICAL—SIGNS AND SYMPTOMS These may be divided into 2 phases: local and systemic. *Local lesions* are found in the skin, the liver, the spleen, the lymph nodes, the lungs and the skele-



FIG. 251 Eosinophilic granuloma. (Same patient as Fig. 250.) Anteroposterior views of both upper femora. Lesions are present in both femora. That on the right involves the femoral neck. Secondary reaction and periostitis are present. The lesion in the left femoral shaft is eccentric and somewhat atypical. There is destruction of the lateral cortex without secondary reaction.



FIG 252 Eosinophilic granuloma. (From Dr M M Pomeranz) Anteroposterior view of left hemithorax. Large multiloculated lesions are present in the posterior portions of the fifth and the ninth ribs. Secondary healing reaction is present. Sclerosis is present. Compare with Figures 48 and 250.

tion and they are of two forms, according to Jaffe⁴—nodular and diffuse. The *nodular* lesions occur particularly in the lymph glands, the spleen and the thymus, the alimentary tract, the skin and the bone marrow. The *diffuse* lesions occur in the pleura, the lungs, the dura, the kidney, the heart and the pancreas. *Systemic reactions* are fever and malaise, the fever being of a persistent low-grade spiking type. There is a secondary anemia and the child's course is downhill until the fatal termination results (Figs 253 to 255). This may occur very rapidly and often does so in a matter of weeks, but sometimes it may take a year or two. Involvement of the base of the skull and therefore of the pituitary-gland region

and the bulbar tissue can be associated with unilateral or bilateral exophthalmos, diabetes insipidus, and other findings suggestive of Hand-Schüller-Christian disease.

In this condition it appears that the resistance of the patient is much less evident than it is in eosinophilic granuloma or Hand-Schüller-Christian disease. As a result the visceral involvement is infinitely more intense than it is in the other forms. The bone lesions, although they do occur in this entity, are relatively secondary because of the very rapid and severe course of this disease.

Nevertheless, bone lesions do occur which in every way are practically identical with those expected in the other two members of this triad (Fig 253).

ROENTGENOGRAPHIC FEATURES. The roentgen findings in Letterer-Siwe disease are apt to be much more intense than those observed in eosinophilic granuloma. Very marked destructive change in one or more areas can be observed (Fig 253). This, however, is not common for the primary change is visceral. Furthermore, the progress of the disease is so rapid that fatal termination before widespread skeletal destruction may result.

It is possible that, since lungs are involved, infiltrative changes can be seen there particularly on the roentgenogram (Fig 254).

Pathology: GROSS APPEARANCE. Grossly the tissue is diffuse or nodular and invades the various tissues mentioned above. There appears to be marked cellularity in this situation with very little fibrous tissue or healing reaction evident. There is little or no lipoid deposition.

Apparently in addition to the nodular lesions that destroy the bone particularly in the metaphyseal area, there appears to be a marked invasion of the marrow which need not show roentgen evidence of destruction. Only on microscopic examination could the degree of extension of the lesion be evident.

MICROSCOPIC APPEARANCE. The basic cell



FIG. 253 Letterer Siwe disease (Figs. 253 to 255 from Dr. Homer A. Graham) Infant 8 months old, admitted June 18, 1948, with pain in the left ear and mastoid swelling for 3 weeks. Low-grade fever persisted with no response to penicillin. The left mastoid area was incised on July 9, 1948, with subsequent continuation of drainage. On July 27, 1948, the left mastoid area was explored and found to be filled with gray-yellow tissue and necrotic bone. A microscopic diagnosis of eosinophilic granuloma was made. Roentgenotherapy was begun. Temperature elevation continued. By August 12, 1948, the infant was jaundiced and the liver found to be enlarged. The prothrombin time was reduced to 18 per cent of normal. A diffuse petechial eruption developed. Peritoneoscopy was performed on September 30, 1948, and showed a firm gray liver with black pigmented spots. A biopsy indicated histologic findings compatible with Letterer Siwe disease. Death ensued on October 6, 1948, but no postmortem examination was performed. The fulminating fatal course had lasted a little over 4 months.

Anteroposterior and lateral views of skull. Note the circumscribed osteolytic lesion behind the mastoid bone. There appears to be another in the vertex. The disease has gone so rapidly to a fatal termination that there has been no healing reaction. Conversely, there has not been time for greater bone destruction to occur.

FIG. 254 Letterer Siwe disease (Same patient as Fig. 253) Anteroposterior view of chest. Infiltrative changes are present in the lung fields. This is presumed to be a reticuloendotheliosis of the lungs clinically diagnosed as bronchopneumonia.



again is a histiocyte. In this instance it differs from the other two diseases of this tribe in that this cell does not contain large amounts of cholesterol esters. Eosinophilic granuloma shows cholesterol esters in the histiocyte in its healing stage and Hand-

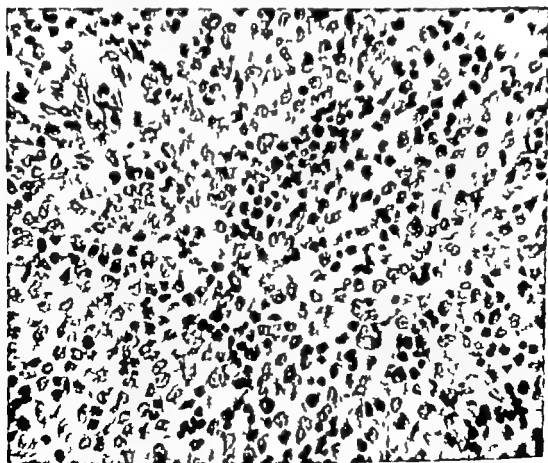


FIG. 255 (Top) Letterer-Siwe disease. (Same patient as Fig. 253) Note focal necrosis. Hematoxylin-eosin. ($\times 60$) (Bottom) ($\times 240$)

Schüller-Christian disease shows continual lipoidification of the histiocyte.

We might consider that histologically Letterer-Siwe disease appears to be practically identical with eosinophilic granuloma except that it is much more diffuse. This is particularly evident on comparison with eosinophilic granuloma in its early stages. The predominating cell pattern in early eosinophilic granuloma and in Letterer-Siwe disease consists of proliferating histiocytes with collections of eosinophils. There is no fibrosis and practically no foam-cell accumulations (Fig 255).

Treatment. There is no specific treatment or any effect which has been observed or described. It has been suggested that corticotropin in eosinophilic granuloma might be useful. Possible extension of this treatment to Letterer-Siwe disease might be considered although reports upon results from the use of this drug in Hand-Schüller-Christian disease and eosinophilic granuloma have not been startling.

Prognosis. Prognosis is poor. This disease usually is very rapid and terminates fatally. The major hope of course is that it may prove to be a phase of Hand-Schüller-Christian disease or at least that the patient may show a resistance to the disease that is characteristic of the reaction to Hand-Schüller-Christian disease.

HAND-SCHÜLLER-CHRISTIAN DISEASE

(Syn. Lipoid granulomatosis of bone)

Historical Notes. In 1893 Hand described this clinical syndrome which may be summed up as follows:

1 Multiple defects in the skull (Fig 256). Subsequent to this there have been added defects in other bones.

2 Exophthalmos.

3 Diabetes insipidus.

4 Other pituitary symptoms such as infantilism, dwarfism and occasionally adipsogenital syndrome which is also termed Fröhlich's syndrome.

In his original report Hand also discussed

the gross pathology of an autopsy specimen of a child aged 3 with particular emphasis upon the yellow spots in the skull which he thought were due to tuberculosis.¹

Schüller² reported 3 cases in 1915. He considered that the symptoms of this disease were related to pituitary dysfunction. Christian³ added another case—that of a 5 year-old girl—in 1919. He also considered this to be primarily pituitary dysfunction.

In 1921 Hand⁴ revised his original conclusion that it might be tuberculosis but also argued against pituitary dysfunction. In 1928 Rowland⁵ referred to the entity as a xanthomatous degeneration of the skeleton. He considered it to be a derangement of cholesterol metabolism. In 1930 Chester⁶ thought that this condition was due to an inflammatory reaction involving the reticulo-endothelial system in bone. He pointed out the histiocyte as the important cell which takes up cholesterol esters and he suggested the name lipoid granuloma of bone rather than xanthomatosis because the diagnosis of xanthomatosis implies a disease of lipid metabolism or a storage type of disease. Since the present term lipoid granulomatosis infers an inflammatory phenomenon today's opinions largely coincide with Chester's conclusions. It is considered an inflammatory disease not a condition related to xanthoma of the skin. A normal cholesterol and the usual absence of skin lesions are considered corroborating facts.

Incidence. This condition has been reported more commonly in males than in females but there is not a great disproportion. It occurs primarily in early life from the first to the tenth year but has been reported in adolescents and even in adults.

Etiology. The etiology like that of Letterer-Siwe disease and eosinophilic granuloma is unknown. It appears that in all three of these diseases the primary cell is the histiocyte and that there is secondary reaction to inflammation of the reticulo-endothelial system. In Hand-Schüller-Christian disease both the bony system and the viscera are involved. In eosinophilic granuloma the bone is affected more commonly.

but in rare cases visceral changes have been observed. In Letterer-Siwe disease the disease is fulminating and widespread. Visceral changes are predominant but changes in bone and skin occur.

With a common cell therefore and an unusual sort of inflammatory reaction it is reasonable to presume (as has been advocated by pathologists such as Mallory⁷) that these diseases are all related and are simply reflections of the same process as it occurs with varying degrees of severity.

Clinical Characteristics: PHYSICAL—SIGNS AND SYMPTOMS. In view of the fact that the skull is primarily and more uniformly in-

volved than other areas cranial symptoms would be most common. Therefore, dysplutiarism is a frequent sign. These latter symptoms include polyuria and polydipsia (diabetes insipidus) thus indicating involvement of the posterior hypophysis. Anterior hypophyseal involvement may produce dwarfism or infantilism. The petrous portion of the temporal bone may also be involved with resultant effective deafness. The local skull lesions will show swelling and at times pulsations and upon pressure distinct sensations of defect in the bone will be felt.

The face may be asymmetrical and ex-

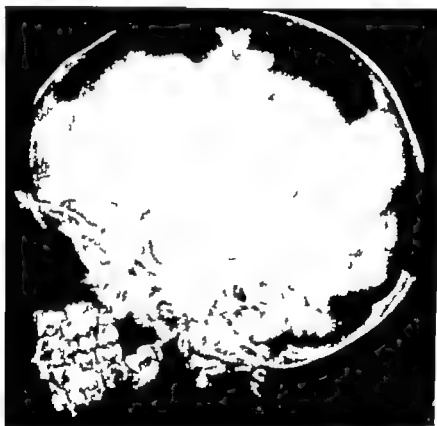


FIG. 256 Hand Schüller-Christian disease (From Dr Eugene P. Pendergrass) White female $2\frac{1}{2}$ years old. Three months history of numerous soft swellings appearing on the head. Downhill course associated with persistent vomiting. Final termination is not known for certain as this patient was lost to observation. Lateral view of skull. There are multiple sharply outlined defects in the skull. The margins of these lesions show an erosion of the surrounding bone which indicates progressive spread. The size of the osteolytic zones is varied. The apparent superimposition in this lateral view indicates widespread dissemination.



FIG 257 Gaucher's disease (Figs 25, to 261 from Dr. M. M. Pomeranz) Lateral view of skull. There is thinning of the tables with increased widening of the diploë especially about the occipital area.



FIG 258 Gaucher's disease. (Same patient as Fig. 257) Anteroposterior view of pelvis and upper femora. Note osteoporosis of the femoral shafts, thinning of the cortex of both femora, poor cancellous bone detail and considerable prominence of the medullary shadows. There are degenerative changes of both femoral necks and heads. The left one shows considerable destruction, the right one shows deformity similar to changes found in Legg-Perthes disease.

ophthalmos unilateral or bilateral is a common phenomenon. Involvement of other bones will be associated with swelling tenderness and defects to palpation there.

The classic description of this condition much like that of Hand is usually a late stage of this disease and earlier phases may simply show a single soft lesion in the skull for instance. Visceral changes may be manifested on the basis of generalized lymphadenopathy, splenomegaly, hepatomegaly and involvement of the lungs and the pleura. Lung changes usually are manifested as a fibrosis. The skin also may be affected by these lipid granulomas but rarely.

CHEMISTRY There is no specific characteristic blood chemical finding, however there may be an occasional leukocytosis or eosinophilia but this is not constant either.

Blood cholesterol levels which are found to range to very high levels in multiple xanthomatosis are not abnormal in this disease or if they are elevated at all there is only a slight elevation.

ROENTENOGRAPHIC FINDINGS The individual lesion is a sharply outlined clear-cut defect in the bone involved. It may be placed deeply in the bone or it may extend

to involve or break through the cortex of a long bone or through either table of the skull (Fig. 256). Schüller has considered that some sclerosis is evident around the periphery but it is not uniformly agreed upon. It is probably impossible to differentiate on x-ray picture alone between this condition and the other two of the triad of this group.

Pathology: GROSS APPEARANCE. There are yellow areas containing dark red interspersed patches. These dark patches are the result of old hemorrhage. In the skull in particular there may be lesions involving primarily the outer tables and under the



FIG 259 Gaucher's disease. (Same patient as Fig. 257) Anteroposterior view of lower femora and knee joints. Thinning of the cortex and patches of medullary cancellous bone destruction are seen in the midshaft and the lower third of the femora. The most striking finding is the bilateral club-shaped widening of the lower femora, the Ehrlenmeyer flask deformity.



FIG 260 Gaucher's disease. (Same patient as Fig. 257) Anteroposterior view of knee joints. Thinning of the cortices, Ehrlenmeyer flask dilatation of the lower metaphyses of the femora and medullary bone destruction are seen.

scalp which penetrate through the cortex (Fig. 256). There also may be lesions on the inner table which erode the cortex on that side and penetrate to lift the dura. Lesions may occur in the region of the pituitary gland produce pressure there and extend forward to the orbital fissures. They are the same type of yellow granulomatous appearing lesions with interspersed patches of hemorrhage scattered through them.

The involvement is not alone of the bony system but may involve the brain, the pleura, the liver, the spleen, the lungs, and the kidneys—rarely the skin.

MICROSCOPIC APPEARANCE. There is evident granulation tissue made up to large degree of proliferating reticulum cells and

their derivative cell, the histiocyte. It is this cell which is the primary cell in this disease and it is this cell which collects cholesterol and becomes a foam cell. When the lesion is healed the histiocyte that has become a foam cell by inclusion of cholesterol begins to disappear and eosinophils also noted earlier disappear. Fibrosis with giant-cell formation that possibly represents coalescence of many small reticulum cells makes its appearance, but there is no bone production.¹⁰

Treatment. X-ray therapy appears to have some effect and curettage of lesions if solitary may be helpful here as it certainly is helpful in eosinophilic granuloma. The disease process in general appears to be a relatively slow, benign but progressive one. Eventually many of the cases terminate fatally but usually from intercurrent dis-

ease. There could be, and there undoubtedly is, fatality that results from involvement of vital organs.

GAUCHER'S DISEASE

Definition. Gaucher's disease is a derangement of lipid metabolism in which kerosin deposition may affect the entire reticulo-endothelial system. This includes bone as well as other tissues (Figs 257 to 261).

History. The first description of this disease was in 1882.¹ The first description of the bony lesions was in 1905.² In 1933 a classic study of this disease including a classification of diseases of lipid metabolism was published.³

Etiology. This disease is part of a general disorder that may, and usually does, involve the entire reticulo-endothelial system.

Kerosin is taken up by the histiocytes of the reticulo-endothelial system. There is some evidence to suggest that this may not be the normal cerebroside kerosin but a glucose-containing variety. At any rate the lipid-filled histiocytes are known as Gaucher cells and are pathognomonic of this disease.

In line with this thought, an interesting summary of pathologic and clinical studies upon a spleen of a 12-year-old girl with Gaucher's disease⁴ revealed that the carbohydrate fraction of the lipid isolated from the spleen was found to be glucose and it was suggested that there may be two forms of lipid disturbance in Gaucher's disease: one in which the lipid is a galactolipid like normal kerosin and the other a lipid composed of abnormal glucose-containing kerosin. Monnier⁵ considers that the disease is characterized by the accumulation of pathologic glucokerosin which is different from normal kerosin.

Clinical Characteristics. There are two types so graded upon the degree of severity. The first is the acute or malignant form that occurs only in early childhood. Death practically always ensues before the end of the first year of life in this type. This form is characterized by spleen and liver enlarge-



FIG 261 Gaucher's disease (Same patient as Fig 257.) Lateral views of both tibiae and fibulae. The right tibia shows enormous dilatation with condensation reaction in the upper half. In the lower half are seen patchy zones of destruction with cortical thinning. The left tibia shows thinning of the cortex and prominence of the medullary shadow.

ment as well as by neurologic symptoms: general hypertonus, increased reflexes, dysphagia, laryngospasm, apathy, and catatonias. Splenectomy is unsuccessful in this type. It may be diagnosed by sternal or splenic punctures. These punctures will reveal the Gaucher cell. Such punctures are successful because the disease is throughout the reticulo-endothelial system.

The greater number of these cases appears to be of the second, more benign type that starts insidiously. 58 per cent in the first decade and 42 per cent between the ages of 10 and 38 years.⁶ These go well into adult life. This group shows splenomegaly, hepatomegaly, changes in the blood picture and bone lesions.

The disturbance of the cellular metabolism in Gaucher's disease is characterized by accumulation and retention of the cerebroside kerosin in the reticular and the histiocytic cells. It is associated with enlargement of the spleen and the liver and at times osseous defects. Pigmentation of the skin, leukopenia, microcytic hypochromic anemia and hemorrhagic tendencies due to thrombocytopenia are found.

ROENTGENOGRAPHIC FINDINGS X-ray findings and osseous localization in order of frequency are as follows: (1) lower femur (Figs 259 and 260) (2) head and neck of femur (Fig 258) (3) vertebrae (4) upper tibia (Fig 261) (5) humerus and (6) skull (Fig 257).

Roentgenographic characteristics are:

- 1 Generalized atrophy of moderate degree
- 2 Coarse-grained spongiosa not differentiated from marrow
- 3 Cancellous bone destroyed either in small well-defined areas with worm-eaten appearance or in large medullary patches
- 4 Cartilage and periosteum are not invaded as a rule. An exception* was a case in which symmetrical involvement of both humeri with penetration of the cortex and invasion of the subperiosteal space occurred. Joints occasionally may be invaded directly.*
- 5 The cortex is usually thinned
- 6 Necrosis, fibrosis and hemorrhage occur from invasion of Gaucher's cells.
- 7 Club-shaped widening of the ends of long bones especially the lower femur occurs. This is referred to as the Ehrlenmeyer flask deformity, one of the earliest and the most reliable signs as disclosed by the x-ray picture.

When the head and the neck of the femur are involved collapse and deformity similar to that of Legg Perthes disease occur. Vertebral bodies collapse but do not infringe upon intervertebral spaces. The skull shows discrete areas of decreased bone density. Pathologic fracture occurs.

CHEMISTRY AND BLOOD EXAMINATIONS. No diagnostic chemical findings are ob-

served. Leukopenia is observed with the leukocytosis found in Pick disease.

Pathology When bone is involved marrow shows diffuse changes with plastic marrow tissue. There are gray areas and interspersed solid gray areas. The cortex appears to outward and thinned by the pressure hyperplastic marrow (Figs 259 to 261).

In the spleen the marrow capillary lymph nodes and the liver large accumulations of Gaucher cells are found. Accumulations also have been found in the posterior lobe of the hypophysis, fundibulum and the hypothalamus.

The Gaucher cell is large, foamy, slightly granular with a small pyknotic nucleus. These cells group and accumulations of them replace the structures of the organ involved. Gaucher cells are filled with kerosin cerebroside.

Differential Diagnosis. This disease must be differentiated from other cases of bone marrow disease. It is differentiated from megaloblastic anemia by the presence of leukopenia. If a lesion is found in bone it is definitely indicative of Gaucher's disease. A leukopenia is also present with Niemann Pick disease. For instance, in Niemann Pick disease the disease is more rapidly progressive and the leukocytosis with no bone lesion is to be expected.

Sometimes the hip lesion, the club-shaped deformity of the femoral head, Legg Perthes disease. The Ehrlenmeyer flask shape of the lower femur will differentiate Gaucher's disease.

Finally, diagnosis may be made by bone marrow puncture when bone invasion is present and/or by splenic puncture.

Treatment. Splenectomy appears not to affect bone lesions. It may improve anemia and will relieve the patient's enormous uncomfortable abdominal distention. X-ray therapy has not produced a beneficial effect.

Prognosis. The malignant infant form produces death, usually within a year. The more usual less virulent form may survive until the sixth decade. Cachexia ev-

develops and the patients die of intercurrent disease

NIEMANN-PICK DISEASE

Niemann-Pick disease is the least common of the diseases due to disturbance of lipid metabolism. A characteristic of this disease is the abnormal storage of phospholipids in the liver and the spleen. Of the three phospholipids (cephalin, lecithin and sphingomyelin) the last is markedly above normal.

A review of 58 cases from the literature showed 13 cases to be strictly familial. Females were afflicted slightly more than males. In 22 cases in the American literature a large proportion of cases were Jewish. Seventeen were females, 5 males. All patients were infants who died before the age of 2½ years—most frequently during the second half of the second year of life. In all cases mental retardation was present. Some children presented cherry red spots in the macula of the retina, a commonly recorded sign of Niemann-Pick disease. This condition with central nervous system involvement with or without Niemann-Pick disease is known as Tay-Sachs disease.

Etiology. The etiology has been considered to be a cellular dysfunction of the tissues rather than storage of lipids taken up from the circulating blood.¹ This is not in agreement with interesting experimental work² in dogs and monkeys and with further work³ in which these investigators succeeded in producing deposition in the tissues of monocyctic cells loaded with phagocytosed lipids similar to the cell accumulations in Niemann-Pick disease. These depositions were produced in the animals by intravenous injections of sphingomyelin. The similarity of findings in these experimental animals to

true Niemann-Pick disease is amazing; this suggests that further research is needed on this subject.

Clinical Features; LABORATORY FINDINGS. The blood usually shows hypochromic anemia with a normal or elevated white count. Blood smears exhibit many lymphocytic elements filled with large vacuoles. This is especially true of sternal puncture. Blood cholesterol is often elevated. Blood neutral fat or fatty acids are always increased.

ROENTGENOGRAMS. The bones may reveal generalized osteoporosis. The picture in bone is least characteristic in this disease of all other lipid-disturbance diseases.

Pathology. The pathognomonic cell is a large clear cell derived from the reticulo-endothelial system and comparable with the Gaucher cell. It is of a more foamy appearance and is without striation. The substance found in this cell and characteristic of it is sphingomyelin, which is soluble in absolute alcohol and stains with Weigert's method for the complex lipids.

Lipoid deposits are found in the histiocytes of all the organs in the body.

Treatment. X-ray therapy, splenectomy and radium appear to be of no avail.⁴ However, it is of interest that a 12-month-old girl with clinical symptoms indicating Niemann-Pick disease was treated with liver extract. Blood cholesterol dropped from 500 to 200 mg. The palpable spleen and liver enlargement disappeared. Presumably complete recovery occurred within 6 months. This case on check up was not clearly Niemann-Pick disease, yet it was some form of lipid disturbance. Enlarged spleen and liver with lipemuria were present. This certainly would appear to justify further trials in proved cases of lipodosis.

Prognosis. The disease is uniformly fatal in almost all reported cases.

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Paget's Disease

(Syn. Osseous dystrophy; osteitis deformans; rarefying osteitis with distortion and thickening of bone; hereditary heterogenous osteopathy)

HISTORICAL NOTES

In 1877 Paget² reported 5 cases of a "rare disease" and included Wilkes' (1869) report of spongy hypertrophy of bone (Fig 262).

This disease cannot be considered rare. Although Paget's description was the first clinical one, it was not even a new disease at that time. Sugarbaker³ indicated that Neanderthal man may have demonstrated the disease. It has been described also in Egyptian mummies. Both the monostotic and the polyostotic forms have been described in recently uncovered remains of prehistoric American Indians. Lesions which simulate Paget's disease have been described in fowl, horses and goats, and fairly typical cases have been found in monkeys.⁴ Deninger⁵ presented the morphologic changes and the roentgenographic evidence of osteitis deformans in prehistoric American Indian skeletons from the Illinois River Valley region. Four of the skeletons showed the generalized form of the disease and one the monostotic variety. Fisher⁶ showed further changes typical of Paget's disease in Indian skeletons. He demonstrated bowing of the tibia and thickening of the diaphysis (Fig 263).

Although Paget was the first (in 1877) clearly to describe the disease, Czerny¹ had used the term osteitis deformans in an earlier publication unknown to Paget. In 1891 von Recklinghausen⁸ included Paget's cases as one variety in a common group of

generalized fibrous osteitis. Throughout the literature since that time there has been much confusion with regard to differentiating Paget's from von Recklinghausen's disease of bone.

It was difficult clearly to separate these conditions until the classical studies of Klenböck⁷ and Schmorl.⁹ These studies tended to clearly differentiate these diseases and finally Mandl's¹⁰ results in von Recklinghausen's disease by extirpation of the parathyroids completed the differentiation.

Paget's² report on osteitis deformans as he termed this condition is still a clear and true description of advanced stages of this disease. However his statements (1) that the disease is usually symmetrical (2) that the limbs no matter how misshapen remain strong and fit to support the trunk (3) that the disease is observed only in patients over 40 years of age and (4) that the disease is inflammatory in nature are not completely the modern concept.

It is true that all of the above tenets go into the making of a typical case, but all of them may be violated and still the patient may have Paget's disease. Brailsford¹⁰ reported one patient with Paget's disease who was 27 years of age. The senior author has seen a patient of 28 years of age with an advanced phase of this disease (Fig 264). Wagner¹¹ reported Paget's disease in an 18-year-old male. In general, however, the disease does occur in patients over 40 and most cases are observed between the ages of 50 and 70.

INCIDENCE

As early as 1915 it was obvious that Paget's disease was not a rare condition.

By that time more than 300 cases had been collected in the literature. However with the advent of routine x ray examination, many more cases came to light.

Schmorl's classic autopsy studies, reported in 1932 have never been equaled in respect to thoroughness and statistical accuracy (see Table 7 on p 329)

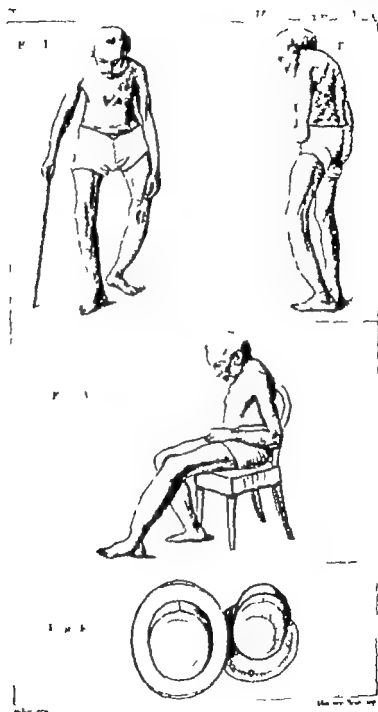


FIG 262 Paget's disease (From Medical Classics 1 55 1936 Baltimore Williams & Wilkins Co) Sketches made of photographs of Sir James Paget's original case. The lower sketch contrasts the patient's hat size in 1844 with that in 1876



FIG. 263 Paget's disease. These prehistoric Indian tibiae show characteristic bone overgrowth and bowing deformity. The sectioned tibia on the left shows a typical overgrown trabecular pattern. From Fisher A. K. Ann Med Hist 7 198 1935)

TABLE 7*

AGE (YEARS)	NUMBER OF AUTOPSIES	NUMBER OF CASES OF PAGET'S DISEASE	PERCENTAGE OF PAGET'S CASES OBSERVED IN ALL AUTOPSIES	PERCENTAGE OF PAGET'S CASES IN RELATION TO AGES
Male				
40-49	340	4	1.18	5.00
50-59	370	16	2.82	20.00
60-69	725	26	3.59	32.50
70-79	442	17	3.85	21.25
80-89	192	15	7.81	18.75
90-100	9	1	11.11	1.25
Unknown	1	1	100.00	1.25
	2,279	80	3.5	100.00
Female				
40-49	248	2	0.80	3.45
50-59	406	10	2.46	17.25
60-69	524	16	3.05	27.57
70-79	805	14	1.74	24.14
80-89	352	14	4.21	24.14
90-100	20	2	10.00	3.45
	2,335	58	2.5	100.00
Autopsies				
Male	2,279		Paget Cases	Percentage
Female	2,335		80	3.5
All cases	4,614		58	2.5
			138	3.0
80 male cases—57.97%				
58 female cases—42.03%				

From Schmorl, G. Über Ostitis Def. rmanis Paget, Virchow's Arch. 283 694 1932



FIG. 264 Paget's disease. (From Dr George Bennett, on whose service this patient was studied by the senior author.) White female, 28 years old. Lateral views of both tibiae. The left tibia shows advanced Paget's disease with considerable osteoblastic reaction and overgrowth.

Numbers of reviews which report many cases are in the literature of these may be mentioned Nichols and Ruines¹² who reviewed 48 cases. Sugarbaker³ who reviewed 51 cases. Brunner¹³ 26 cases. Newman¹⁴ 82 cases. Brailsford¹⁵ 154 cases. Wood¹⁸ 130 cases. Delitala¹⁶ 110 cases. Dickson¹⁷ et al., 367 cases and many other reports throughout the literature almost too numerous to mention in which as many as 1 to 5 cases are reported.

The incidence with regard to sex is of interest because of possible tie-up to aberrations in the sex hormone picture which might be presumed if the disease state were found to occur predominantly in one sex. This is not so however because in the literature although a moderate edge is given to males there is a very large number of cases

among females. This is borne out by the authors' experience. Furthermore most cases in either sex have a perfectly normal sexual history and studies of 17 ketosteroids and urinary estrogens are not grossly out of line.

In 51 cases Sugarbaker³ reported the incidence of males to females as 3.2. Brunner¹³ in 26 cases reported 19 male to 7 female. In 154 cases Brailsford¹⁵ noted 82 males to 72 females.

Paget's disease has been reported in more than one member of a family in many instances.¹⁷ Parkes, Weber and Huber¹⁸ reported the disease in three sisters. Koller¹⁹ presented two family trees in which Paget's disease had occurred as 3 cases in one and 2 in another which can be considered as beyond mathematical probability of mere chance. Furthermore he found 27 other families in the literature with more than one Paget's case. In 3 such families 4 clear-cut Paget's cases were found. In 7 families, 3 cases each were recorded. In 17 families, 2 cases each were reported.

Geographic location may or may not have significance. It is possible that it is described only infrequently in China²⁰ because of lack of thorough medical checkup rather than because of location or dietary habit. The literature contains case reports from practically every locale in the world.

Seasons appear to have no particular relationship primarily because this disease is of chronic type requiring years to develop into its full blown phase.

DISTRIBUTION

This disease process in one report or another has been described in every bone in the body including the metatarsals and the metacarpals. Conversely the most disseminated polyostotic cases show uninvolved areas a fact which led Albright²¹ to refer to this as a localized bone disease with widespread distribution rather than a generalized bone disease such as hyperparathyroidism.

This is an important concept. Generalized



FIG. 265 Paget's disease. White female 66 years old. Anteroposterior and lateral views of left tibia. Roentgenograms of February 22 1954 reveal an early osteolytic phase of Paget's disease in the lower third of the tibia. A complete short oblique undisplaced fracture line is retouched and is indicated further by the arrows. Treatment consisted of immediate application of a plaster boot with attached walking heel and the encouragement of full weight bearing despite initial pain.

Roentgenograms of June 16 1954 indicate no progression of the Paget's disease process. In fact, there is healing reaction in the cystic tibial lesion. This case is one of many which confirm the authors' opinion that trauma does not cause progression of Paget's disease. Moreover, if functional activity is maintained osteoporosis is avoided. Note, incidentally, a comparatively rare instance of Paget's disease involving the calcaneus.

bone disease is exemplified by osteitis fibrosa generalisata or osteomalacia. In these conditions gross or microscopic changes will be noted throughout the skeleton.

Paget's disease on the other hand is a localized or (as the authors prefer to describe it) a disseminated process. When it is widespread and progressing some areas even of involved bones will be unaffected. Albright²¹ reported one case in which all bones were involved. This is exceptional and probably would still fulfill the above tenet. The incidence of localization in the varying parts of the skeleton has been

well outlined by Schmorl⁸ with whose autopsy data the authors' clinical experience coincides. Schmorl⁸ in a report of 4 614 autopsies (1932) found this disease to be distributed as follows: (1) sacrum 56 per cent (2) spine 50 per cent (3) right femur 31 per cent (4) skull 28 per cent (5) sternum 23 per cent (6) pelvis 21 per cent (7) left femur 15 per cent (8) clavicle 13 per cent (9) tibia 8 per cent (10) rib 7 per cent and (11) humerus 4 per cent. The extra percentage above 100 per cent merely indicates that numbers of his cases had multiple involvement.

The conclusion is that those portions of the skeleton most subject to stress and strain show the greatest incidence of involvement.

ETIOLOGY

It is of great interest to follow the myriad listings of the etiology of Paget's disease. Only in a condition in which the etiology is as yet unknown could so many far fetched causes be listed.

For years this disease was confused with von Recklinghausen's hyperparathyroidism. The final disassociation came about only after Mandl⁹ reported the effect of parathyroidectomy upon von Recklinghausen's disease. Yet despite the immense amount of work done in the field of bone metabolism since that date no clear-cut etiologic factor for Paget's disease has been uncovered. It is of interest to review various thoughts that have been advanced in regard to etiology.

1. **Trauma.** A few instances have been cited in which Paget's disease is alleged to follow trauma. A typical report is exemplified by Spota²² who described a T fracture of the lower end of the humerus sustained in a traffic accident by a male of 28. Subsequently Paget's changes appeared in this area.

Lièvre²³ stated that in some cases of monostotic Paget's disease trauma may have preceded its development.

Snapper²⁰ observed monostotic Paget's disease of the tibia in a male of 29 a few years after a football accident.

Lewin²⁴ indicated trauma to be an aggravating factor. He indicated rapid progress of the disease after trauma even in early cases of Paget's involvement. The probability is that he did not realize the degree of osteoporosis that follows simple immobilization of bones involved by this disease (Fig. 265). He therefore confused such osteoporotic changes in the x ray picture and assumed them to be actual progression in the disease.

Attempts to relate this disease to trauma

occur only a few times in the literature whereas the overwhelming opinion in numbers of reports does not relate this disease to trauma.

In regard to those cases cited above for sake of completeness "one swallow does not make a spring. Obviously trauma is infinitely more frequent in occurrence than Paget's disease. So actually any cases so related are probably simple coincidence.

It must be remembered that very early Paget's-disease change may not be shown clearly on x ray examination or by chemical examination yet the involvement of a bone area by this process makes it more susceptible to fracture. There are thousands of cases reported in the literature in which there has been no established relationship to trauma. The senior author has observed cases of this disease with injury—even fracture—in normal bone areas which never developed osteitis deformans changes. The authors state unequivocally that there is no evidence to indicate that trauma is an etiologic agent. Would that the etiology were so simple!

2. **Vitamins.** Avitaminosis A has been advanced as an etiologic factor in Paget's disease. One case of alcoholic liver disease which showed abnormal vitamin A studies as well as Paget's disease is cited.²⁵ On the basis of this an elaborate theory postulating involvement of the reticulo-endothelial system in bone marrow and especially the liver is presented.²⁶ According to this report²⁶ since the reticulo-endothelial cells, particularly of the liver are the site of the conversion of carotene to vitamin A, avitaminosis A is postulated as the etiologic agent in Paget's disease. Therapy therefore is indicated to be prolonged administration of vitamin A.

Studies on 6 cases of Paget's disease²⁷ showed very low serum vitamin A values. When vitamin A was given calcium was depressed from 14.5 to 12 mg per 100 cc. In other words when the Paget's-disease cases had hypercalcaemia vitamin A reduced it. These workers considered that there was a relationship between low vitamin A liver

disease and Paget's disease. In the authors' experience hypercalcemia does not occur in Paget's disease except on bed rest or after immobilization. They have not noted any particular therapeutic advantage derived from vitamin A administration. Snapper²⁰ reported that in parts of North China where severe avitaminosis A is the rule, very few cases of Paget's disease are observed. In spite of all this, studies on vitamin A and other phases of liver and reticulo-endothelial function are being carried out by the authors.

It also must be remembered that excess vitamin A can produce changes of cortical thickening in bone. This has been reported in children. It is actually the result of toxic intakes of this substance. In a way these changes of vitamin A overdosage can be likened to some phases of Paget's disease (Fig. 246).

3. Endocrine Disorders. Endocrine disorders with parathyroid dysfunction²¹ also thyroid and adrenal derangements have been advocated as etiologic factors.

It is primarily of historical interest to recall that Ballin²² in 1933 clearly felt that hyperparathyroidism was responsible for Paget's disease. Although work done by that time disassociated these disease states, this attitude only highlighted the common opinion of the day. It must be remembered that this was close to the time of Mandl's report⁸ in 1926 on the effect of parathyroidectomy upon von Recklinghausen's disease, and many workers felt that this was the answer to most bone disturbances.

Conversely, Zimmer²³ thought that the disease was due to lack of parathyroid hormone and in 1930 he advocated the use of this hormone in the treatment of the disease.

Gutman and Parsons²⁰ clearly separated Paget's disease from hyperparathyroidism. Observers since then, including Relfenstein and Albright²¹ have concurred in this differentiation. Of interest was the argument of Relfenstein and Albright²¹ in 1944 against an endocrine or a metabolic back-

ground which they based on the fact that this disease is spotty, not generalized in distribution through the body. Yet, in their book²¹ they described a case in which all the bones of the body were involved. The patient refused study and there was no proof that the entirety of each bone was involved as would occur in an endocrine disturbance. In the authors' opinion it could have been a metabolic disturbance with a spotty but ever widening distribution like that of arteriosclerosis.

Coste²⁴ indicated some association with ovarian function, reporting an increase of the disease symptoms following oophorectomy and relief of symptoms with stilbestrol. Such procedures, however, have not resulted in improvement of other cases.

Thyroid administration has been a failure in treatment, and the presence of a hypothyroid or a hyperthyroid state in association with this condition is at best coincidental. Furthermore, most of the thyroid studies were those made prior to radioactive iodine pick up and protein-bound iodine studies.

4. Inflammation. Paget's² original contention was that this was a chronic inflammatory lesion because of the hyperemia of the marrow of affected bones on macroscopic examination.

Knaggs²⁴ thought that absorption of toxins was responsible. Thaler²⁵ considered the disease to be an inflammatory morbid process, a nonspecific chronic osteitis developing from focal lesions.

No one has ever shown clearly that organisms or their toxins play any part in this disease, even in its most advanced state. The hyperemia first observed by Paget and confirmed by others is in the authors' opinion most likely a nonspecific reaction to dead and dying bone tissue or is evidence of arteriovenous shunts.

5. Heredity. Moehlig²⁶ reported upon 40 cases and attempted to relate the disorder to familial diabetes, obesity and tallness. A family history of diabetes was observed in 13 of 40 cases. Thirty-three cases had one

or more members of the immediate family who were 71 or more inches in height 30 cases had one or more members of their family who weighed 200 pounds or more 12 of the 40 cases had nodular goiter

Parkes Weber¹⁸ indicated numerous occurrences of this disease in a single family and Koller¹⁹ in an analysis of Paget's disease cases demonstrated that mere chance could not explain the family occurrences as regards mathematical probability

In 1889 it is interesting that Paget²⁷ in a publication 12 years after his first description of the disease wrote 'I have not known it in two members of the same family Many have had gouty ancestors but I do not think more than the equal number of persons in the same rank of life In his first report,² however he reported no familial gout The authors frequently have seen this combination of gout and Paget's disease

Hereditary stigmata reported coincident with Paget's disease have been retinitis pigmentosa, angiod streaks of the retina and diabetes²⁸

In the senior author's experience many cases of Paget's disease have been observed in which one or more members of the same family have the disease Furthermore it can be demonstrated in numbers of his cases that parents have also demonstrated the disease—whether due to hereditary predisposition alone cannot be said at this time Some fault in differentiation of normal tissues predisposing to the development of this disease when normal physiologic processes slow with advanced age can well be an hereditary factor

6. *Vascular Changes.* Loeper²⁹ opposed the hypothesis of those who consider it a coincidence that Paget's-disease changes in bone and calcification of arteries and arterioles frequently are demonstrable in the x ray picture Such vascular changes he presumes to be primarily responsible for the Paget's-disease changes in bone It is considered that vascular calcification usually is not limited to areas where bone changes took place but frequently occurs in distant

regions However both diseases may be due to a common factor

Gaenslen⁴⁰ considered that arteriosclerosis might be a contributing cause to this disease. He indicated however, that arteriosclerosis is a common finding in the age group in which Paget's disease is predominant.

In 1945 Edholm et al.,⁴¹ reported a most interesting vascular disturbance which they thought was common in Paget's disease. They referred to this as a high cardiac output secondary to excessive vascularity of bone. In their opinion the vessels in Paget bone acted like arteriovenous aneurysms. They confirmed the frequency of high pulse pressure and cardiac enlargement previously reported by Kay et al.,⁴² in 1934 These workers had also noted severe arteriosclerosis in Paget's disease

Confirmation of extreme vascularity of Paget's-disease bone simulating multiple arteriovenous aneurysms was demonstrated by Edholm et al.,⁴¹ by establishing high cardiac output. The method involved studies by the Lewis-Grant plethysmograph together with observation of signs of cardiac failure—notably high pulse pressure and venous congestion. These plethysmographic studies indicated that there was a great increase in blood flow through bone affected by Paget's disease The figures were that the peripheral blood flow through the diseased bone using the nutrient artery of the humerus was 20 times normal. These authors inferred from this increase in peripheral blood flow a corresponding increase in cardiac output They reported a cardiac output of 13.3 liters per minute whereas the normal should be about 4 There was also elevation of skin temperature overlying the affected bones and evidence of cardiac failure

In a case of advanced Paget's disease they applied a tourniquet to an extremity markedly affected by the disease. The pressure was maintained above the systolic. Then they catheterized the right aortic. Following the application of the tourniquet

pressure they noted four things: decrease in right auricular pressure, slowing of the pulse, decrease in cardiac output and slight increase in diastolic pressure. These are the same responses that follow partial occlusion of the afferent vessel of an arteriovenous aneurysm. Therefore they concluded that Paget's-disease bone is the site of multiple arteriovenous shunts.

This is a reasonable consideration because elevation of local temperature in such bone has long been noted. Furthermore on microscopic section, it is observed that the haversian canals dilate and actually become lost in baysian lakes. There is a uniform shift of normal marrow to fibrous marrow especially where the disease is active. Further more blood supply in bone ends in sinusoids which by dilatation could give back pressure phenomena.

Storsteen and Jones⁴³ did further vascular studies in Paget's disease. They used arteriography which demonstrated increased vascularity adjacent to Paget bone. It failed to demonstrate arteriovenous aneurysms. In one case they demonstrated increased femoral venous pressure and increased femoral venous oxygen saturation on the involved side. This was considered as presumptive evidence of arteriovenous communication despite negative arteriography.

There has been considerable current interest in the relationship of Paget's disease and cardiovascular disease. A very complete review of the literature and 54 case studies were presented by Sornberger and Smedal⁴⁴ who concluded that the coincidence of cardiovascular disease appears to be greater in extensive Paget's disease than among the general population even of the same older age group.

The principal cardiovascular manifestations are cardiac enlargement and arteriosclerosis.⁴⁴ Cardiac enlargement was related to the following findings in Paget's disease singly or in combination: (1) increased cardiac output as a result of diffuse involvement of the skeleton with marked vascularity of affected bones; (2) the afore-

mentioned arteriosclerosis which affects the myocardium or its valves; (3) osseous deformity of the cervicodorsal spine and rib cage which is common in polyostotic Paget's disease. This in itself may compromise the pulmonary circulation and help to induce right heart failure; (4) accompanying hypertension in association with vessel calcification peripherally or in the kidneys.

The evidence of circulatory disturbance was such as to lead Sornberger and Smedal⁴⁴ to the conclusion that all patients with extensive osteitis deformans should be considered as having "potential heart disease" (New York Heart Association Criteria).

Throughout the literature as the above attests vascular and even cardiac disturbances have been observed in relation to Paget's disease. The arguments range that vascular disease is a cause that it is a coincidence that it is a result or a sequel to Paget's-disease involvement of bone or that it may be a part of a common causal factor for the production of both disease states.

Whichever of these hypotheses may be operative it appears without question that the incidence of vascular disease is higher in Paget's-disease cases than in the general populations of like age.

Furthermore it is apparent that Paget's disease occurs usually in the age period when vascular deterioration is expected to occur.

We know that bone has limited ways to react to injury. The piling up of periosteal bone in osteomyelitis as a reaction to inflammation and necrosis is well known. So too may we presume excessive reaction of bone in a diffuse pattern if it is widely affected.

Pathologic material of osteitis deformans shows a mosaic appearance of bone—a crazy-quilt of new and old bone forms most actively in a meaningless pattern. The fatty marrow becomes fibromarrow. True cysts are not observed. What appear to be cysts are acellular spaces and often are considered to be the results of infarcts.

If we assume a diffuse vascular disease



FIG. 266 Paget's disease. White male 57 years old. Anteroposterior and lateral views of lumbosacral area. Note diffuse Paget's disease involving the fifth lumbar vertebra and the upper sacrum. There are simultaneous osteolytic and osteoblastic reactions. This is the commonest site of Paget's disease according to the autopsy records of Schmorl.³

process affecting bone in the manner of arteriosclerosis affecting the vessels of the body we can imagine an interesting sequence. The condition would then be a wide spread one with multiple local vascular plaques. Just as arteriosclerotic plaques can cause infarction of a soft tissue area disturbance of minute circulation areas in bone could cause change there.

Ham⁴⁴ has emphasized the relatively inefficient mechanism of bone nutrition beyond the capillaries. Nutrition of both cancellous and compact bone is felt to occur by means of diffusion of tissue fluids through the lacunar spaces and the canaliculi.

Ham states that the effective operation of a tissue fluid diffusion system requires that no bone cell in any bone form can be more than a fraction of a millimeter from a capillary. By inference then if the feeding vessel to a group of capillaries or to a capillary is interrupted this extremely tenuous blood supply to the end point (i.e. the bone cells) will be lost. This would result in death of the area no longer supplied by the blood.

Tissue necrosis would induce hyperemia. This latter would cause excess bone reaction and formation particularly with release of natural bone inductor substances from dead and dying bone. So side by side would de-

velop a jigsaw puzzle of old and new bone with little of the normal modeling. The reaction of the entire bone with hyperemia would stimulate periosteal reaction and overgrowth as in osteomyelitis, particularly of the low-grade type.

7 Mineral Disturbances. Moeller⁴⁵ and later Roholm⁴⁶ reported frequent incidence of Paget's disease among workers subjected to fluorine inhalation over long periods of time. Changes are uniform sclerosis of bone and ossification of tendinous insertions. However according to Brailsford⁴⁷ these changes are more granular and are symmetrical in all afflicted parts of the skeleton.

Paget's disease is not usually symmetrical and may be monostotic. Furthermore Wolff and Bauer⁴⁸ did experimental work with fluorine poisoning and also studied the fluorine content of bones in 6 well-defined cases of Paget's disease. These were found to be lower than normal in value. The conclusion therefore is that chronic fluorine intoxication cannot be an etiologic factor.

Disturbances in phosphorus and calcium metabolism except for negative balance in the predominantly osteolytic stage and positive balance in the osteoblastic phase have not proved significant as etiologic factors in Paget's disease.

8. Mechanical Factors. Stress and strain

play a part in the development of this disease. It is not proved that they are causative factors alone but the involvement most frequently of the skeletal parts most subject to stresses cannot be dismissed lightly (Fig 266). Schmorl's statistics are from 4 614 autopsies with thorough study of the skeleton. Not only did he note involvement mostly of bones subject to stress and strain he also noted that the changes were more common at tendon and ligament attachments to the bone. The probable explanation of skull changes is in the very powerful muscles of mastication. Osteoporotic areas persist mostly in the skull away from muscle and tendon attachments.

CLINICAL FEATURES

Paget's disease is a clinical syndrome implying the development of a deforming osteitis which in turn is responsible for the symptoms and the signs by which the disease is known. There are two supposed types: a monostotic form and a polyostotic form. The probabilities are that the monostotic form is possibly only a stage of the polyostotic form—i.e., although a monostotic form may be observed throughout life the probability is that microscopic changes at least will occur elsewhere. Certain it is however that varying stages of the disease may be observed. The bowed, deformed, almost anthropoidlike stance and appearance described so classically in 1877 by Paget² is familiar to everyone (Figs 262, 284). The less marked type with involvement of fewer bones is perhaps not so familiar a picture and yet with the aid of x-ray studies more and more of these less generalized and relatively undeformed cases are being diagnosed. The conclusion is that these cases by far outnumber the classical form.

Schmorl* in routine careful autopsies maintained that 3 per cent of all individuals show evidence of Paget's disease although the changes may be only microscopic.

Paget's disease is common especially in an aging population. It frequently causes varied and oftentimes disabling symptoms.

These symptoms often are attributed to other causes and the Paget's disease dismissed as an incidental finding. For most clinicians consider it mysterious and not to be affected by any known therapy. In other words Paget's disease is often observed on a gastro-intestinal series or an intravenous urogram. The tendency is simply to note it and to do or recommend nothing for it. It has been the authors' experience that these patients' symptoms may be the result of the Paget's disease and that they can be made more comfortable and some effect upon the disease obtained. This will be discussed in detail under treatment. (See Table 8 p. 468.)

Physical—Signs and Symptoms. The principal symptoms produced in Paget's disease are (1) aching bone pain, (2) increased warmth of a part, (3) headache, (4) hardness of hearing, (5) dizziness, (6) stiffness, (7) weakness, (8) easy fatigue, (9) pain on weight bearing, and (10) visual disturbances.

This disease may be relatively asymptomatic for months to years especially during its early phases. In the authors' experience however one or more and often all of the above symptoms will be noted at one time or another in all patients. The symptoms depend upon the areas involved. For instance skull involvement may be absent in many cases throughout their life. In such an instance no headache, eye or hearing disturbances resulting from involvement of this area are to be expected. Often the long bones are affected. The process may remain mild for an indefinite time. On the other hand the disease may involve the long bones diffusely and severely. Again in the former instances little complaint may be evident in the latter instance trouble may be considerable such as pain, deformity or fracture.

Therefore in considering symptoms one must keep in mind the areas of involvement and the degree of involvement. One can be certain that symptoms in an area will occur when the involvement is widespread in that area.



FIG. 261. Paget's disease. White male, 39 years old. Anteroposterior and lateral views of right tibia, illustrating a typical advancing wedge going from above downward in its course. The foremost portion of the wedge is osteolytic. Behind this area the rest of the upper two thirds of the tibia has been overgrown by an enormous osteoblastic reaction.

Certain general symptoms are observed in all cases of Paget's disease. These are a general stiffness and a tendency to become easily fatigued. Often also these patients will exhibit a tendency to somnolence. These symptoms may occur even when the skull is not involved. When these patients are immobilized for any length of time especially if the disease is widespread symptoms of hypercalcemia also may occur due to severe bone absorption of immobilized part.

Objective signs of the disease are (1) warmth of an involved part, especially of the tibia, where bone is close to the surface (2) deformity (3) increased head size (4) enlargement of bone structures in



FIG. 268. Paget's disease. White male, 39 years old. Anteroposterior and lateral views of right femur. In the femur the characteristic osteolytic wedge advances from below upward. In its wake there follows a severe osteoblastic reaction in the distal femur. The anteroposterior view is a composite of 2 roentgenograms taken on the same day.

involved (5) increased fragility of bone and frequent fracture (6) limitation of joint motion (7) simian appearance with broadening and flattening of chest with kyphosis, shortening of torso, prominence of pelvis in relation to waist, bowing of extremities in both lateral and anterior planes often in the combined plane (8) eye signs because of actual changes in the orbit and (9) auditory and vestibular signs due to changes in the petrous portion of the temporal bone.

PATHOLOGY

Before discussing the gross and the microscopic pathology it is important to view the over-all pattern of this disease.

The primary phenomenon in Paget's dis-

case is an osteolytic process which may be in the form of a large advancing wedge taking up gradually increasingly large amounts of bone substance so that eventually (as in the tibia for instance) we see it extend to encompass the entire shaft in its transverse diameter (Fig 267) Furthermore we see this wedge advance from above downward until the entire longitudinal length of the shaft becomes involved Occasionally in the femur we may find an advancing wedge which appears to go from below upward but, in the authors experience the pattern in the tibia is always from above and downward (Fig 268)

Immediately following this advancing wedge is a very extensive osteoblastic reaction (Fig 268) leading to a dense heavily trabeculated bone structure of irregular pattern.

In the gross form of bone involvement of major type particularly in the long bones there are recurrent transverse infarctions these are actually fracture lines (Fig 269) They present an area of bone dissolution on the convex surface and an area of condensation on the concave surface It appears that these are both a result of a bowing process and that they contribute to further bowing of the involved bone

A second type of reaction rather than the advancing wedge is a multiple and diffuse type of osteolytic change such as that which is observed in a vertebral body This is usually associated with immediate reactive osteoblastic effect (Fig 270) Some cases however may progress rather to an advanced degree of osteoporosis from the osteolytic effect, particularly in the vertebral bodies with little change as concerns condensation of bone (Fig 271) As a rule however reaction and bone proliferation occur very soon after the bone destructive effect in these instances also

In those cases in which the osteolytic effect is widespread and severe with little osteoblastic reaction compression of the vertebral bodies is a common phenomenon. There may be platyspondyly or flat ver-



FIG 269 Paget's disease White male, 61 years old. Anteroposterior and lateral views of tibia. A linear transverse fracture of the tibial shaft is present. It is repeated and recurrent fractures of this type at one site which gradually result in bowing deformity It is also such fractures which unquestionably are associated with much of the pain in Paget's disease.

tebral bodies which are quite widened in the transverse dimension and decreased in their vertical dimension. There may be cod fish-like vertebrae as observed in osteoporosis of the postmenopausal type and there may be compression fractures of the usual and typical wedge type (Fig 271)

A final form must be considered this was observed and reported upon by Schmorl¹⁴—in particular in the lumbosacral area—and is one of the reasons why Schmorl reported such a high incidence of Paget's disease in general autopsy groups (Fig 266) This form shows multiple minute areas of osteolytic reaction associated with the osteoblastic response and the typical microscopic changes of the mosaic pattern. This mosaic pattern



FIG. 270 Paget's disease. White female, 58 years old. Anteroposterior and lateral views of lumbar spine. The process involves the third and the fourth lumbar vertebrae. Marked osteoblastic reaction is indicated by dense longitudinal trabeculations and even more condensed trabeculations which outline these vertebral bodies and by the relatively radiolucent areas between the abnormally sclerotic areas.

of course is diagnostic of all Paget's disease. Change of this sort may be fairly diffuse in an involved bone and yet so microscopic that it will not be noted except on such examination.

The over all effect on bone when there is massive involvement by Paget's disease is to produce a considerable enlargement of the bone involved. This enlargement appears to fall in a pattern of low-grade bone destruction associated with low-grade bone formation with still evident differentiation of zones of compact and cancellous bone and still definable medullary shadows. All of these three areas however will be much broadened and distorted (Fig. 272).

Periosteal proliferation will also be present and much increased. Just as periosteal proliferation occurs so too does endosteal

proliferation occur, it is observed as a parent and usually partial obliteration of the marrow cavity. It occurs because of fibrous-tissue reaction and because of proliferation of wild irregular poorly formed bone formation (Fig. 273).

Throughout this bone too, will be zones of small cystic areas which are true cysts but which appear like small spaces. These spaces are found to be filled with debris and fibrous tissue. Scattered throughout the bone will be zones of excessive density which may be quite hard (Fig. 273). Such scattered areas of excess density will be observed in all cases of Paget's disease even in those which are primarily osteolytic and which can be cut easily with a knife.

Flat Bones. The pelvis shows an incre-



FIG. 271 Paget's disease. White female 40 years old. Anteroposterior and lateral views of lower dorsal and lumbosacral spine. The sacrum and the upper pelvis are involved by a severe osteolytic process. The lumbar and the dorsal spine appear dense on the anteroposterior view. This, however, is an optical illusion because the correct exposure for the radiolucent pelvis and sacrum is too small for the dorsolumbar spine. The lateral view allows for a more uniform exposure. It can be seen here that the osteolytic process in the lower dorsal and lumbar spines is extreme. There is little osteoblastic response and much vertebral deformity and collapse are present. The twelfth dorsal vertebra shows over all collapse. The third, the fourth and the fifth lumbar vertebrae show severe biconcave compressions or codfish-tail appearance. These changes are precisely like those of severe osteoporosis. Compare with Figures 136 and 141. See Figures 295 and 308 in relation to this patient's later course.

broadening and thickening (Fig 274). The vertebral bodies will show an increased broadening, flattening, concavity or wedging (Fig 275). The scapulae will show broadening and thickening similar to that observed in the pelvis (Fig 276).

Skull changes may be of the circumscribed porotic type such as Schüller¹⁰ described as osteoporosis circumscripta which in essence is really only a widened or more rounded advancing wedge similar to that observed in long bones (Fig 277). When such an osteo-

porosis circumscripta condition is observed there will be in this area multiple plaques of condensation and numerous small cystic areas. These become better differentiated as the disease progresses. The osteoporosis circumscripta as seen in the skull and in the long bones is not an actual hole. It is still bony structure although there is considerably more porosity than in other bone areas. One will observe wide trabecular spaces which are filled with fibrous material.

Changes in the skull however need not

follow the osteoporosis circumscripta pattern. The eventual end is the same (Fig. 278). Whether it starts as osteoporosis circumscripta or whether it starts (as it often does) in the pelvis with a multiple not circumscribed but diffuse osteolytic reaction the pattern then progresses to osteoblastic reaction and the eventual condensation and thickening of bone (Figs. 279-280).

We then observe marked widening of both the inner and the outer tables of the skull with some widening of the diploë. The outer table, not having the pressure of the brain substance upon it to keep a relatively smooth molded appearance, becomes quite irregular and raised and gives rise to the "kinky woolly" appearance that is so char-

acteristic of advanced skull change (Fig. 280).

Long Bones. The long bones will tend to develop bowing deformities which are not in a single plane but three-dimensional in a double plane. For instance a bow not only will be anterior but also will be anterolateral. This is particularly evident in the femora and the tibiae but is observed also in the upper extremities especially the upper humeri (Fig. 281).

One must bear in mind that in the skull, as well as in the long bones the process may become arrested at almost any point for an indefinite period of time and not progress further. As a matter of fact Schmorl⁴ described a case in which actual healing of the



FIG. 272. Paget's disease. White male, 65 years old. Lateral view of skull. There is marked overgrowth yet one can still define the very thick inner table, the diploë and the thin outer table. It is of interest that the inner table has expanded in an outward direction since pressure of the brain substance usually preserves the inside dimension of the skull in Paget's disease.



FIG 273 Paget's disease. White male 52 years old (*Left*) Lateral view of left tibia (1935) Periosteal proliferative reaction is seen at the lower third of the tibia posteriorly and at the mid third of the tibial shaft anteriorly. The periosteum is so raised in the latter area as to appear to be the wall of a cyst. Endosteal proliferation is shown by obliteration of the medullary shadow in the lower half of the tibia (*Center and right*) Anteroposterior and lateral views (1942) Anterolateral bow is present. The lesion has now progressed by constant interplay of osteolytic and osteoblastic processes to a typical Paget's-disease appearance

process occurred. On the other hand the whole gamut may occur finally to produce the most widespread fulminating thickening and change.

When Paget's disease involves bone whether the skull or other areas the change may be associated with so much osteoblastic reaction that the bone is very thick, very hard and very heavy (Fig 282). Yet it may be almost like too rich concrete and easily

crumble and crack. On the other hand the process may be predominantly osteolytic with little osteoblastic reaction. In these instances the skull or other bones similarly involved will become very thick, appear like the very hard type and yet be quite soft, will cut easily and will be very light in weight (Fig 281).

Strangely, fractures are as likely to occur in the dense, heavy type as in the porotic



FIG. 274 Paget's disease. White male 59 years old. Anteroposterior view of pelvis. Osteoblastic type of reaction with severe deformity. This is reflected in the abnormal shape of the pelvic inlet. The acetabula are deepened and the heads of both femora are proportionately deformed. The iliac wings are broadened and flattened. The lower lumbar spine is altered in appearance also.

light type the obvious reason therefore being that there is more flexibility and give in the porous or osteolytic type. Conversely there is more fragility in the dense type because there is much less elasticity. It is more brittle therefore.

Microscopic Pathology In the active phase much of the reaction appears to occur in the haversian systems. Multinucleated giant cells reabsorb bone in an expanding fashion. The reabsorption occurs as a result of osteoclast reaction. This produces thin bone trabeculae particularly in the cortex. The haversian canals become enlarged to the point that they appear to be haversian lakes. This results in wide communication of the haversian areas with the medullary canal. At this point it is difficult to determine a zone of demarcation between com-

pact and cancellous bone. A type of fibrous bone comes into being. Soon after there is a reaction of the marrow as well as of the bone. The fatty marrow becomes ischemic and then fibrosed. It appears that this process is like an ischemic hemorrhagic necrosis.

This disease process appears to initiate a tissue reaction of hyperemia which causes an increased rate of absorption of bone. Then with the production of further bone defect by intensive absorption and cavitation fibrosis occurs. During this phase the process extends into the subperiosteal area and there too produces a fibrous-tissue reaction which is a precursor of periosteal proliferative bone reaction.

The above refers to the osteolytic or active stage. We may go further in this active stage and indicate that during it endosteal

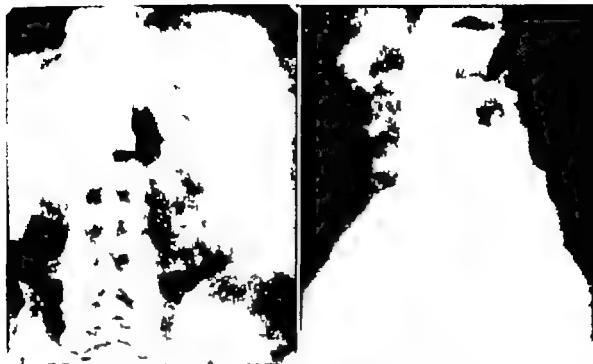


FIG. 275 Paget's disease. White male 59 years old. Anteroposterior and lateral views of lumbar spine. There are generalized mixed osteoblastic and osteolytic changes in the vertebral bodies. Biconcave compression of the vertebral bodies has occurred with associated broadening and flattening. The second lumbar body presents a typical codfish-tail appearance. The intervertebral disks have herniated into the softened bodies.

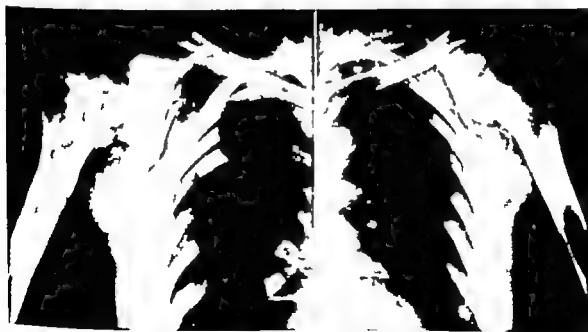


FIG. 276 Paget's disease. White male 59 years old. Oblique views of both shoulder girdles. The scapulae are deformed, the right one being quite dense and deformed as a result of malunited fractures. The right humerus shows advanced osteolytic and osteoblastic Paget's disease. The left scapula is also thickened. The body of the scapula just below the glenoid appears to be cystic. The left humeral head is involved only moderately.



FIG. 277 Paget's disease. White female 54 years old. Anteroposterior and lateral views of skull. This is a classical example of a well-deprived zone of osteoporosis *circumscripta*. It involves the frontal area and enters the temporal area bilaterally. The lateral view shows an area of condensation reaction high in the frontal zone. This is an osteoblastic response to the initial osteolytic process.

new bone formation is minimal and the disease advances rapidly throughout the involved area of bone structure. The endosteal reaction is a transitory one and is followed by a metaplasia into characteristic Paget bone* (Fig. 283). This comes about through the process of a precursor fibrous tissue which differentiates into thin soft, fibrous bone trabeculae. These are not to be confused with the later-appearing deranged lamellar bone which forms the mosaic pattern. Everywhere however the disease process appears to be confined by a periosteal proliferative reaction which appears to be of two forms: one is the new formation of subperiosteal lamellae and the second is the formation of thick osteophytic proliferations derived from the cambium layer of the periosteum. The second type is pre-dominant.⁸

This process described herein in the active stage is particularly dramatic as it is observed in the long bones. A similar reaction, except that one must bear in mind that compact bone is not so thick in flat bones, occurs in the flat bones such as the pelvis and the scapulae. Similar reaction is also evident in the vertebrae and the skull.

This active stage of osteolytic change is described for purposes of clarity. However one must bear in mind that a true and complete osteolytic change never occurs by itself. Almost simultaneously in association with the osteolytic phase is an osteoblastic reaction which varies in degree. This osteoblastic reaction has been referred to as a healing reaction. It is a healing reaction but a healing reaction of the most completely disorganized type that can be imagined. It is because of this combination of a very active disorganized healing reaction simultaneously observed with very active osteolytic changes that the wildly disordered bone so aptly described by Schmorl⁹ as a mosaic pattern results. Furthermore this pattern appears to be unique for Paget's disease.

The osteoblastic reaction again must be visualized as running the gamut from the

most abnormal type of bone formation to relatively normal. In some areas the healing reaction may result in relatively normal bone with the usual type of cement lines with good lamellar bone form and with reasonably well shaped haversian systems. However the general rule is for a very disorganized bone to be formed with no regular pattern no clear-cut haversian canal system nor any apparently normal bone trabeculae or normal-appearing cement lines. In fact as a rule in the osteoblastic reaction the cement lines are not thin as in the normal bone but are thickened and heavy. This thickened cement line actually occurs because it happens to be the zone of inter-

section between contiguous areas of disorganized abnormal trabeculae (Fig. 283).

The net consequence here is the development of brittle bone which has resistance to compression greater than the osteolytic bone but lacks the elasticity and the resistance to shearing and angular forces.

SUMMARY As a final evaluation of the multiple types of change that may occur in Paget's disease of bone it is possible to sum up the situation as follows: it is an osteolytic process associated almost at once with osteoblastic reaction. As the process persists a predominant shift goes first from that of an osteolytic reaction to an osteoblastic one. In all the bones involved and



FIG. 278. Paget's disease. White male 62 years old. Lateral view of skull. Osteoblastic reaction to osteoporosis circumscripta. There are two zones of osteoporosis circumscripta: one in the frontal area and one in the occipital area. The osteoblastic responses are twofold in type. First is condensation evident within the osteolytic zone of the frontal region. Second is a very marked condensation reaction arising *de novo* and occurring in the temporo-parietal area between the two zones of osteoporosis circumscripta. However osteoporosis circumscripta can involve the entire calvaria followed by uniform osteoblastic reaction throughout.

In any areas of the bones involved all possible combinations may occur. Under these circumstances gross as well as microscopic variations of the disease will be evident.

A great enigma in the underlying problems of bone physiology is why do we have so much osteolytic change in this disease and such remarkable osteoblastic effect? What is its significance? Actually the unrequited osteoid evident in Paget's disease is so great that we find in this condition the highest levels of recorded serum alkaline phosphatase values. One can presume the possibility of an inductor substance. In the presence of dead or dying bone severely affected in a widespread fashion by such an osteolytic phase, it is also quite possible that a hyperemia results as a reaction to this dying bone. This plus the release of an inductor substance would easily result in extremely active bone formation reaction.

When the healing reaction does occur however one would assume that it would follow some sort of organized pattern as is usual in normal states. In this condition, however the enigma is that it does not do so. This leads one to the presumption that some irritative phenomenon must be going on that keeps this disorganization active.

X-ray Findings. X-ray examination remains the best method of determining the characteristic features of Paget's disease as well as for following the progress of the disease. The entire pattern of this disease of the skeleton can be followed quite accurately on the roentgenogram.

The disease is characterized by an osteolytic process closely followed by an osteoblastic reaction. These changes often occur nearly simultaneously and there may be variation in the degree of either osteolytic or osteoblastic reaction as well as in the



FIG. 279 Paget's disease. White male 49 years old. Lateral view of skull. The diffuse osteolytic process involves most of the calvaria. It has been followed closely by multiple discrete osteoblastic islands. The tables of the skull show considerable thickening.

degree of admixture of both (Figs 273-281)

For clarification it is best to consider the processes separately. Then one can visu-

alize combinations which occur on x ray examination

The osteolytic phase may occur as small single or multiple areas of bone absorption

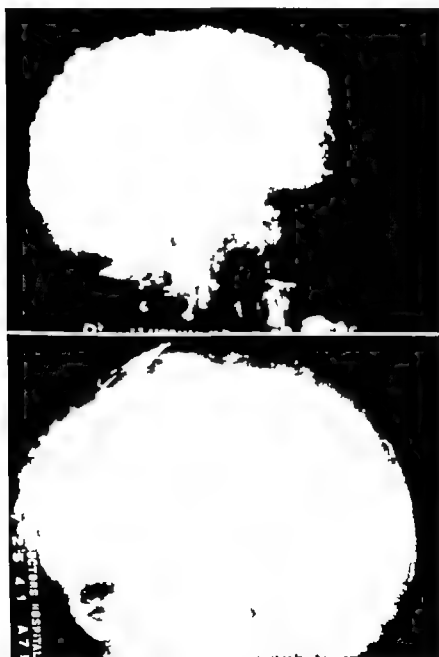


FIG 280 Paget's disease. White female 42 years old. (Top) Lateral view (1936) of skull. This is a more advanced type of Paget's disease than that shown in Figure 279. There are so many islands of bone condensation that they appear to be coalesced into a solid mass at many points. Yet here and there between these dense areas, one can note small osteolytic zones. (Bottom) Five years later (1941) considerable increase in osteoblastic response is evident. This has resulted in bony overgrowth of the inner and the outer tables as well as involvement of the base of the skull.

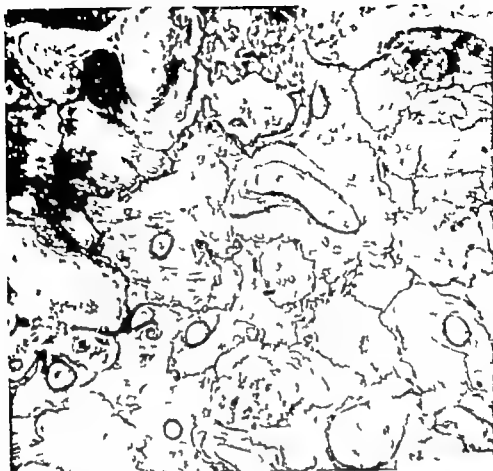
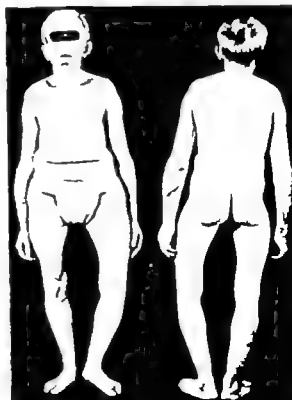


FIG. 283 (Top) Paget's disease. Note the mosaic lines in the bone. Hematoxylin-eosin. ($\times 60$)

FIG. 284 (Right) Paget's disease. Note the moderately enlarged head with the prominent forehead. The clavicles are thickened, prominent and enlarged. The torso is shortened. The pelvis is broadened. The femora and the tibiae show bowing deformity of both the anterior and the lateral type.



localized. The diffuse form becomes manifested by dense major trabecular patterns which in general follow the lines of stress in the bone involved (Figs 287-296). On magnification the x-ray picture also reflects minor irregular trabecular patterns in the background admixed with the above (Fig. 274). This corroborates the previously noted wild bone formation reaction which constitutes the mosaic pattern.

The localized type of osteoblastic reac

tion presents areas of bone condensation of varying size (Fig 288). These may be referred to as isolated areas of hypercalcification. This reaction in particular at times has been confused with metastatic changes, especially from the prostate. Careful evaluation of the x ray picture as a whole with attention to the osteolytic phase also will help to differentiate Paget's disease from metastatic carcinoma of the prostate (Fig 288).

Various structures of the skeleton differ in architecture. Therefore this disease process will vary in appearance radiographically in relation to the structures it involves. We may divide the skeleton into areas in which uniform patterns of disease occur. These may be listed as (1) the skull (2) the ribs

and the clavicles, (3) the spine (4) the scapulae and the pelvis (5) the long bones of the *extremities* and (6) the tarsal and the carpal bones.

1 THE SKULL. The greater changes are observed to take place in the outer table from the very beginning of the process. At least three basic phases of reaction may be seen.

The most common change is that of multiple osteolytic areas associated with immediate contiguous osteoblastic reaction. These combined areas coalesce to form ever widening patches of Paget's bone until the entire skull becomes affected. With this reaction, the outer table in particular becomes thickened and the diploë becomes largely obliterated (Fig 280). Because of the pressure of



FIG. 285 Paget's disease. (From Dr. Walter R. Peterson.) This case is of particular interest since areas of osteoporosis circumscripta are observed in the skull and the pelvis simultaneously. Lateral view of skull. A large zone of osteoporosis circumscripta, an osteolytic phase of Paget's disease, is seen in the fronto-temporo-parietal area. A second zone, smaller in size, is observed in the occipital region.

the brain substance upon the inner surface of the inner table this remains smooth in contour except for sharply outlined vessel markings. The outer table which has no molding pressure to confine the bone changes bursts outward in an exuberant woolly-appearing bone reaction. This disease does not respect suture lines as they become obliterated as involvement progresses (Fig 280)

Another not uncommon form but one which perhaps has been overemphasized is osteoporosis circumscripta described by Schüller.¹⁰ Sosman¹¹ examined a trephine specimen from the skull of an original case described by Schüller. The pathologic findings revealed an absorptive phase of Paget's disease. Schüller¹¹ later conceded that the two were related. It starts more commonly in the frontal or the frontoparietal area.

This has been referred to as the monophasic type.²² It is not a single separate phase of Paget's disease but simply one of the manifestations of this disease. It represents a single ever widening confluent area of osteolytic reaction (Figs 277 278 285). This type of bone absorption induces osteoblastic response. Unlike the more common sequence described above where there are multiple smaller osteolytic zones the osteoblastic reaction to osteoporosis circumscripta may be years in developing fully (Fig 289). The usual sequence in the skull is for the porotic circular area ever to enlarge until the entire calvaria is affected.

As the osteoporosis circumscripta lesion spreads over the calvaria seemingly largely to involve the outer table condensation appears at the periphery. Then islands of dense new bone appear scattered throughout



FIG 286 Paget's disease. (Same patient as Fig 285.) Anteroposterior view of pelvis. Both iliac wings and inferior pelvic rami show zones of osteoporosis circumscripta with dense osteoblastic reaction surrounding them.



FIG 287 Paget's disease White male 49 years old Anteroposterior view of pelvis and hip joints The osteoblastic response in the head and the neck of the left femur almost follows the stress pattern of the calcar femorale. Note the dense osteoblastic reaction in the right pelvis.

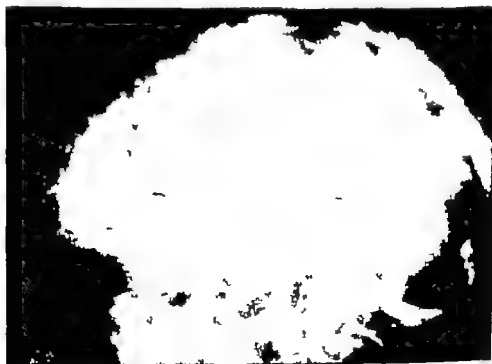


FIG 288 Paget's disease White male, 70 years old. Lateral view of skull. Cannonball osteoblastic reaction to pre-existing osteolytic Paget's disease. There are a flattening of the anterior and the middle fossae and a definite convexobasia.

the area of bone absorption. These osteoblastic responses continue until a full blown typical Paget's-disease skull is observed. This too shows the picture of marked hypertrophy of the outer table with multiple warty excrescences, obliteration of the

diploë and a smooth inner table presenting prominent vessel markings (Fig. 289).

The third type of skull change is the direct result of the osteolytic process upon the base of the skull. With softening of bone structure in that area the weight of the

FIG. 289 A and B. Paget's disease. White female 49 years old. Anteroposterior and lateral views of skull (1942). On the anteroposterior view (A top) there are marked overgrowth and density of bone in the right frontal and parietal areas. Scattered across the fronts of the skull can be seen numerous dense islands of bone. In the left frontoparietal area there appears to be some persistent osteoporosis circumscripta. The lateral view (B bottom) shows a large central zone of osteoporosis circumscripta involving the frontal, the parietal and the occipital areas. This has crossed suture lines. It is separated from the remaining normal occipital area by a sharply outlined margin. The frontal and the parietal areas show an osteoblastic response to marked degree with increased density of the inner and the outer tables and obliteration of the diploë. The petrous portion of the temporal bone shows an osteoblastic reaction.





FIG 289 C (Top) Lateral view of skull (1944) Extension of the zone of osteoporosis circumscripta well into the occipital area has occurred.

FIG 289 D (Bottom) Lateral view (1950) The entire calvaria has been involved by the osteolytic process with further healing osteoblastic response in the frontal region.

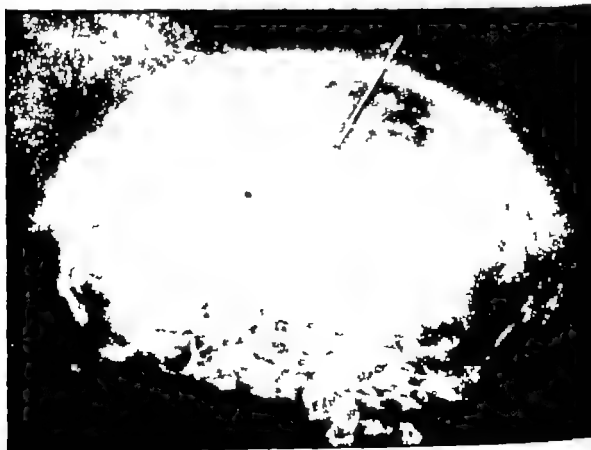




FIG 290. Paget's disease. White male 48 years old. Anteroposterior and lateral views of skull. This is an example of leontiasis ossea resulting from Paget's disease. There is advanced osteoblastic new bone formation involving both maxillae, the base of the anterior fossa and the mastoid area. This patient had advanced typical Paget's disease involving the pelvis.



FIG 291. Fibrous dysplasia. (From Dr M. M. Pomeranz) Lateral view of skull. There is supra-orbital overgrowth simulating leontiasis ossea. Note the circumscribed lesions of fibrous dysplasia in the calvaria.



FIG. 292 Hyperostosis frontalis interna. (Seen in consultation on the medical service of Dr. A. I. Rubenstein) White female, 54 years old. Anteroposterior and lateral views of skull. There is a characteristic bone-formative reaction involving the inner table of the frontal bones. The new bone plaques have a dense wavy outline. This is presented because it is important in the differential diagnosis of osteoblastic skull lesions such as occur in leontiasis ossea due to osteitis deformans, fibrous dysplasia and osteopetrosis. More than 9 out of 10 cases of hyperostosis frontalis interna occur in females. There may be associated endocrine changes, including diabetes mellitus, mental symptoms and hypertension.



FIG. 293 Paget's disease. White male, 61 years old. Clavicle. Periosteal and endosteal new bone formation have resulted in marked over all enlargement.

FIG. 294 Paget's disease. White male 48 years old. Lateral view of lower lumbar spine. The fourth lumbar vertebral body shows very early osteolytic and simultaneous osteoblastic response. This produces a vertebra of considerably increased density without derangement of over all architecture.

FIG. 295 Paget's disease. White female now 53 years old. Compare with Figure 271 taken 13 years earlier. This patient was not observed or upon controlled therapy during the period 1944 to 1954. Anteroposterior and lateral views of lumbar spine. The essentially osteolytic process in the lumbar spine has resulted in complete herniation of the intervertebral disks into the soft vertebral bodies. This resulted in contact of the margins of the bones and bridging of the vertebral bodies. This has been followed by complete coalescence of the third the fourth and the fifth lumbar and the first sacral vertebrae. A similar process occurring in the cervical spine is observed in Figure 315.





FIG. 296 Paget's disease. White male, 69 years old. Anteroposterior view of pelvis. This is essentially an osteoblastic Paget's disease with dense areas in both iliac bones and the ischial bodies. The pubic bones and the pubic rami show osteolytic change as yet unreplaced by osteoblastic reaction. The ischial rami and the ischiopubic junctions show an intermediate mixed osteolytic and osteoblastic picture. It is of interest that an osteoblastic reaction in the upper shaft, the head and the neck of the femur shows dense trabeculations distributed along the lines of stress. Contrast with Figure 286. There is moderate narrowing of both hip joints, indicating a hypertrophic arthritis that is a frequent complication of deforming Paget's disease.

skull and its contents causes a telescoping of the spine into the skull. The collapse of the softened base of the skull has been referred to as *convexobasia*²³ but more recently this type of deformity has been referred to as *platybasia*²⁴ (Fig. 288). This condition produces encroachment upon the spinal cord by a deformed foramen magnum which often produces neurologic disturbances (to be discussed under Complications).

The widespread changes of the base of the skull may and often do encroach upon any of the cranial nerve foramina.

Occasionally marked involvement of the maxillary bone or bones may occur and when this becomes profuse with marked condensation and proliferative reaction it could expand to the nasal bones and the zygoma. A leonine facial appearance, referred to as a *leontiasis ossea*, results (Figs. 290-291-292).

There has been considerable controversy as to whether or not *leontiasis ossea* is a phase of Paget's disease alone or whether it represents a separate bony condition (Fig. 290). It is quite likely that this condition

can also result from involvement of these structures by polyostotic fibrous dysplasia (Fig 291)

Furthermore this type of appearance and change in the skull has been observed in association with Paget's disease involving the skeleton elsewhere. The presumption is therefore that Paget's disease can be a major cause of this condition

2 THE RIBS AND THE CLAVICLES Changes in the ribs and the clavicles do occur and are usually of the multiple porotic type closely followed by osteoblastic reaction. The end result is bowing deformity and over-all enlargement of these bones (Fig 293). The sternum may be similarly overgrown

In addition, the normal obliquity of the ribs lessens. This results in over-all enlargement of the chest with seeming elevation of the ribs

3 THE SPINE. The spine may show involvement of a single vertebra, of several vertebrae or even of all the vertebrae (Fig 270). When a single vertebra is involved it is usually quite dense and is referred to as an ivory vertebra because of its density (Fig 294). This finding is often considered to be a metastatic lesion from the prostate. This may be true at times. Differentiation would then be on the basis of sex and chemistry

Frequency of involvement ranges from below upward—that is to say the lumbosacral area is involved most commonly, the cervical spine least so (Figs. 266 and 315)

The changes usually observed in the spine are diffuse multiple osteolytic foci often associated with considerable osteoblastic response (Fig 275)

If the healing reaction is slow to occur and is only moderate in degree the vertebrae involved will show changes precisely like those observed in severe osteoporosis: there will be wedge compression type fractures in the dorsal area and biconcave compression of vertebral bodies in the lumbar area (Fig 271). Sometimes the bones are so softened that platyspondyly or widening



FIG 297 Paget's disease. White male 40 years old. Anteroposterior view of pelvis and lumbar spine. The pelvis shows an osteolytic reaction in the iliac wings. The margins of the pelvic inlet show periosteal reaction with little or no condensation. There is a mild osteoblastic reaction in the acetabular areas. This should be contrasted with the dense osteoblastic appearance of the lumbar spine. Yet even these dense trabeculae in the lumbar spine are quite spongy and coarse

and flattening of the vertebrae occurs (Figs 270, 271, 275). The disk spaces usually are preserved. Rarely they may be absorbed and coalescence of the involved bodies may occur (Fig 295)

When the spine is a focus of a severe osteolytic process with little healing, neurologic complications are frequent.

Marked healing reaction of vertebrae affected by Paget's disease is common. The trabeculations may appear very coarse and sparse. When a single vertebra is involved



FIG 298 Paget's disease White male 68 years old. Anteroposterior view of pelvis. This is an intermediate type termed by some as amorphous. It contrasts with the severe osteoblastic form of Figure 296 the osteoporosis circumscripta of Figure 286 and the spongy predominantly osteolytic picture of Figure 297. The right half of the pelvis and the upper right femur show a diffuse osteoblastic reaction with poor trabecular detail. There is a large bone island adjacent to the lower end of the right sacroiliac area. The left side of the pelvis apparently has been the seat of a more severe osteolytic process. It shows very poor osteoblastic reaction in the wing of the ilium. The major healing reaction is localized in the region of the left hip joint where the stress factor is greatest. Its spotty appearance with bone islands, indicates that the healing is of poor quality. There is a moderate degree of acetabular protrusion, hip-joint narrowing and femoral head and neck deformity. These are somewhat greater on the left than on the right side as one would expect from the aforementioned description.

it may be difficult to differentiate it from hemangioma of the vertebra (Fig 294). As a rule the trabeculae are numerous and dense. Magnification demonstrates numerous other trabeculations of less well-developed appearance. Some proliferation of bone is often present and actual invasion of the spinal canal with neurologic complications may occur.

4. THE SCAPULAE AND THE PELVIS The scapulae and the pelvis show similar reac-

tions to invasion by this disease process (Fig 276). The pelvis is affected much more commonly. The type of involvement is usually multiple foci of absorption with wide spread bone formative response (Fig 296). Occasionally an osteoporosis circumscripta phase is clearly observed in these areas too (Fig 286).

Radiologists have differentiated late changes in these bones by referring to them as the spongy or amorphous type.⁴⁵



FIG. 299 Paget's disease. White male 62 years old. Anteroposterior and lateral views of left leg. The entire tibia is involved by Paget's disease with severe osteoporosis present in the proximal half and a poor grade of healing in the distal portion. There appear to be some cystic changes in the lower third of the tibia. The mid-tibia is the site of an antero-lateral bow. A transverse fracture line can be seen in the mid third on the lateral view. There is excess bone reaction on the concave side of the bow. The fracture line is hardly apparent here but is more obvious on the convex side of the bow. This infers that such fracture lines will increase the bowing deformity as they heal.

Actually study of such changes clearly shows that the spongy type is merely a severe osteolytic form with little healing response (Fig. 297). On the other hand the amorphous type demonstrates exuberant healing reaction (Fig. 296). Not only are there dense trabeculations, but also discrete condensed bone islands (Fig. 298).

Again, we can prognosticate deformities



FIG. 300 Paget's disease. White male 60 years old. Anteroposterior view of both forearms. There are overgrowth and thickening of the right ulna, particularly at its distal third. There is a mixed osteoblastic and osteolytic Paget's disease of the distal end of the left radius extending into the styloid process. There is bone formative reaction in both carpal areas. This patient had widespread Paget's disease.

of these bones. If the phase is primarily osteolytic, there is poor resistance to compressive force. Such deformities as protrusion of the femoral head into and through the acetabulum as well as compression of the pelvic inlet will be observed (Fig. 274). The pelvic inlet will become narrowed and triangular in shape. The pelvic outlet may also be encroached upon. The obturator foramina may become deformed. If the disease affects one side more than the other asymmetry can result.

The degree of proliferation of bone in this disease may be so great as to obscure the sacro-iliac joints (Fig. 274).

5 THE LONG BONES OF THE EXTREMITIES

The long bones may all be involved. The lower extremities are affected more commonly than the upper and the femur is affected more commonly than the tibia except in the so-called monostotic type. In that group the tibia is involved more commonly. In the upper extremities the humerus is involved more commonly than the radius and the ulna (Figs. 276-300). Al-

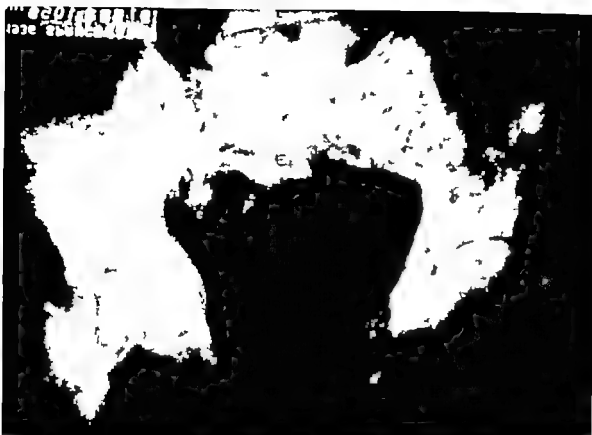


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FIG 301 Paget's disease. White male 60 years old. Lateral views of both ankles and feet. There is advanced osteoblastic Paget's disease in the left talus. Very early trabecular coarsening is observed in the left calcaneus and the rest of the tarsal bones on the left. On the right, there is a more advanced stage of Paget's disease with trabecular coarsening in the calcaneus. Milder changes are seen in the rest of the tarsal bones and the proximal metatarsals.



FIG 302 Paget's disease. White male 61 years old. Anteroposterior and lateral views of right tibia. The zone of demarcation between Paget's disease of advancing wedge type and normal bone is at the healed fracture line. There is good alignment here after treatment in a walking plaster boot.

though the metacarpals and the phalanges may be affected this is very rare

The distribution and the stage of involvement may be haphazard. In other words the humerus on one side may show change and the radius or the ulna on the other. Similar variations in regard to the lower extremities also may be observed. One bone may be the site of an advancing osteolytic wedge actually an osteoporosis circumscripta, of a long bone. Usually following closely at the heels of the advancing wedge osteoblastic filling in will be noted. This is different from the picture in the skull in that there is not so great a time lag (Figs. 267-268)

Still other bones may be the site of the multifocal lytic lesions associated with bone formation reaction (Figs. 273-281). Considerable emphasis has been placed upon the advancing wedge yet in the authors' experience for the long bones the diffuse process is the more common one.

Changes throughout a long bone may sometimes be observed almost from the very beginning. Often however the involvement begins at one end or the other and progresses until the opposite end of the bone is reached.

When a long bone is involved by a widespread process bowing deformity, marked thickening and overgrowth of the bone occur (Fig. 264).

At the major point of convexity infraction lines with some bone absorption will



FIG. 303 Paget's disease. White male 54 years old Anteroposterior and lateral views of femur (A) On the anteroposterior view there is visible a thin incomplete transverse fracture line. It is at this point that the complete fracture occurred following trauma. (B) Complete fracture occurred in the mid-shaft of the femur after the fall (C) The fracture is well aligned and fully healed 3 years later

often be observed (Figs. 269-299). These infraction lines are transverse. On the concave side there will be increased density. These represent transverse fracture lines. It appears therefore that such fracture lines, usually multiple, may be both a cause and an effect of the bowing.

The bowing deformity is usually compound combining both anterior and lateral bow (Figs. 264-273). The authors never have observed a medial bow and only very rarely a posterior bow.

The appearance of the bone architecture will be compatible with the degree of osteolytic change and the degree of healing (Figs. 267-268-299). If the former predominates a coarse spongy thickened appearance is to be expected. If the healing effect is marked very dense eburnated bone that is distended and thickened will be observed (Fig. 282).

In all types of involvement of long bones by Paget's disease periosteal thickening, areas of hypercalcification and scattered cysts will be observed (Fig. 273).

6 THE TARSAL AND THE CARPAL BONES
The tarsal and the carpal bones may be

involved; however, these rarely are affected (Figs. 265-301). The osteolytic process is usually overshadowed by dense bone trabeculations. These bones show a condensed or eburnated appearance.

COMPLICATIONS

Complications of Paget's disease range from the natural sequelae of the disease itself as a local manifestation to general derangements of body physiology. In addition, the skeletal changes make the bone susceptible to fracture and to malignant supervision.

For simplicity, we may divide these complications into local and general ones.

LOCAL COMPLICATIONS

These include fractures, deformities, pressure phenomena, basilar impression, and malignant supervision.

Fractures. Fractures represent the most common complication. In 130 cases of Paget's disease, Wood²⁴ described 19 fractures. Of these 11 were of the femur, 4 of



FIG 304 Paget's disease. White female 55 years old. (Left) Anteroposterior view of pelvis. Mixed osteoblastic and osteolytic Paget's disease is present in the pelvis, the lumbar spine and the upper femora. Note the compression and the deformity of the pelvic inlet and the third lumbar vertebral body. There is an incomplete fracture line in the transcervical region of the right femur. (Right) Lateral view of right hip joint. The fracture line of the right femoral neck is more clearly shown. Treatment in this case consisted of continued ambulation on crutches without weight bearing. Today one should consider internal fixation.



the humerus 1 of the radius and the ulna and 3 of the tibia and the fibula.

If one considers the enormous numbers of infarctions or microfractures then almost every case of this disease at some time will show fractures. The microfractures are of little consequence in relation to treatment. They result in pain and varying degrees of

FIG 305 Paget's disease. White female 66 years old. Lateral views of right femur. Typical transverse fracture of the junction of the upper and the middle thirds of the right femur. Note the old malunited fracture of the lower portion of the femur. This had been treated elsewhere some years before in Russell's traction. The authors' approach to complete fractures in the long bones has been intramedullary fixation. In this instance Küntscher nailing was made more difficult by the previous malunion and a short nail was used.



FIG 306 Paget's disease. White male, 38 years old. Anteroposterior and lateral views of upper tibia. (Left) Lateral view of the upper tibia shows a zone of osteoporosis circumscribing the tibial tubercle. (Center) Avulsion of the tibial tubercle has occurred at the upper portion of the involved area. (Right) Postoperative roentgenograms show replacement of the avulsed tubercle and screw fixation, and finally, follow up study indicates satisfactory position 3 years later. Subsequently, the avulsion reoccurred and required an additional procedure similar to that shown in Figure 318.

disability. However, displacement commonly does not occur in this type of fracture. Healing occurs within a few weeks, and the pain due to the fracture recedes (Figs. 265, 269, 299). Often these fractures may be observed at the distal end of an advancing wedge (Fig. 302).

Most commonly, these microfractures are located at the center portions of the bowed bones. The convex surface shows a zone of dissolution of continuity; the concave side shows condensation (Figs. 269, 299). It appears that these microfractures occur as a result of shearing forces in a bowed extremity. It is also reasonable to presume that once they have occurred, some moderate separation on the convex side will occur so that healing will eventuate in increased bowing.

When a microfracture occurs in an important weight-bearing bone, the pain may be such that the patient will reduce activity or stop weight-bearing (Figs. 265, 269). Additional osteoporosis will increase the fracture tendency, and such a patient may

develop a complete and even displaced fracture (Fig. 303). The authors have observed this phenomenon in the past. It is so impressive that they firmly believe that x-ray pictures of all cases of advanced Paget's disease should be carefully made if a complaint of additional or increased pain occurs in any long bone (Fig. 303).

Careful roentgenograms usually will demonstrate microfracture or a seemingly incomplete fracture line. If present, either intramedullary fixation or the application of a walking cast and insistence upon careful activity and weight bearing is indicated (Fig. 302). Functional activity will aid in reformation of bone substance and healing. The complication of complete fracture in this disease therefore is often one that can be anticipated and prevented with proper measures (Figs. 265, 269, 304).

Paget's-disease bone is more susceptible to fracture than normal bone. Therefore, direct trauma is more apt to result in breaking of this brittle or soft bone. This would be true even if no incomplete fracture or

microfracture pre-existed. Complete fractures in Paget's-disease long bones are transverse. The commonest sites are the upper third of the femoral shaft and the tibia (Figs 305-316).

It must be recalled that this disease is commonest where forces are most active. Therefore in addition to other areas it is found at attachments of tendons to bone, the so-called apophyses. When the process about the site of the tibial tubercle is osteoporotic, as not infrequently occurs, avulsion of this tubercle may occur (Fig. 306).

Fractures in this disease will heal as well as those in normal bone. If they are approximated and if weight bearing is encouraged from the earliest possible moment. Too long immobilization of the part will result in severe absorption of bone from the injured part, then release of excess calcium into the blood stream with symptoms of hypercalcemia may well occur. Immobilization of

the total patient even more surely will produce hypercalcemia and its sequelae.

Deformities. It appears that the abnormal type of bone produced by Paget's disease does not retain normal resistance to deformation. In itself therefore deformities especially of the bowing types must be expected (Fig. 273). As mentioned above fractures also may contribute to deformity. This results from increased bowing, an effect of microfractures, also from malunion after complete fractures and displacement (Figs. 269-299-305).

Other deformities of involved bones occur as a result of thickening and overgrowth, as illustrated by the increased head size and the prominence of facial bones to produce leontiasis ossea.

Compressive forces will also deform involved bones. This is exemplified by crushing phenomena as observed in the vertebral column (Fig. 307).



FIG. 307. Paget's disease. White male, 48 years old. Anteroposterior and lateral views of lumbar spine. There are severe biconcave compression and avulsing of the third lumbar vertebral body which shows advanced Paget's disease. The adjacent vertebrae are free of this disease.

FIG 308 Paget's disease. White female 43 years old. The patient developed progressive signs of paraplegia over an 8-year period. The neurologic level was at the twelfth thoracic dermatome. Myelogram demonstrated a complete block at the tenth thoracic vertebrae. Laminectomy was performed from the ninth thoracic to the first lumbar level. The bone was greatly softened. The dura was open and the spinal cord was found compressed against the posterior dura. The usual cause of difficulty in this and similar cases is encroachment upon the spinal cord by collapsed Paget's bone from the involved area. The decompression of the wide laminectomy resulted in almost complete recovery of this patient.

Lateral view of dorsal and lumbar spine. The arrow indicates the point of greatest collapse at the tenth thoracic vertebra. Biconcave collapse is also present in other vertebral bodies. See Fig. ures 271 and 295.



Pressure Phenomena. Other local complications are invasion of foramina at the base of the skull through which the cranial nerves make their exits. Therefore we may list visual disturbances from encroachment upon the optic nerves and the chiasm.³⁷ This causes atrophy of the optic nerve.

Two other eye complications have been noted. They are pigmented corneal degeneration,³⁸ and cataract located in the cortical rather than the central portion of the lens. It is felt this latter is a type characteristic of an endocrine origin rather than of senility.³⁹ There is also a high incidence of a senile type of chorioretinitis.⁴⁰

Involvement of the petrous portion of the temporal bone results in impairment of hearing, a frequent complication of Paget's disease. It is of interest that although the vestibular apparatus is in this region too generally there is no particular disturbance of equilibrium. The deafness observed in this disease is usually otosclerotic. Although others are not in agreement,⁴¹ some authors⁴² have suggested that otosclerosis may be a

monostotic form of Paget's disease. These authors⁴¹ reported upon microscopic preparations of the petrous portions of the temporal bone showing that the normal elongated trabeculae are replaced by an irregular mass of thin bone spicules apparently due mainly to osteoclastic decalcification with a hasty reconstruction leading to an incomplete remodeling of the bone structure. This abnormal destruction and rapid formation associated with an additional extensive fibrosis of the marrow produced considerable destruction of the osseous labyrinth and impaired hearing.

Pressure phenomena produce severe problems when the spine is involved. The changes in bone are of several types as indicated above under pathology and radiology.

To sum up the dorsal spine is more commonly involved by compressions. These may be wedge type as observed in osteoporosis or they may be a flattening of the entire bone so-called platyspondylitis. Some cases particularly when marked collapse of bone occurs develop cord-compression signs and

even progress to paraplegia (Fig 308). These are results primarily of an osteolytic phase of Paget's disease. Other cases develop similar neurologic symptoms and signs but result from actual pressure of new bone formation which is part of a marked osteoblastic response.

These changes often are observed in the dorsal spine and will improve with laminectomy. Such surgery is indicated in severe collapse and in the proliferative type (Fig 308).

Milder forms of both types have been observed by the senior author to improve with good bracing and magnesium therapy.

Basilar Impression. (Syn. *Platybasia*,⁴¹ *convexobasias*.⁴²)

This deformity is a telescoping of the cervical spine into the basilar area of the skull (Figs 288-97). It may occur as a result of congenital or developmental anomaly. It also may occur as a result of softening of bone in the basal area, the form resulting from conditions like Paget's disease, osteomalacia or hyperparathyroidism.

HISTORICAL NOTES. The condition was described in 1844 by Rokitsansky⁴³ and further detailed studies were made by Virchow⁴⁴ and Grawitz.⁴⁵ Neurologic disturbances were first related to postmortem findings



FIG. 309. Paget's disease with development of sarcoma. White male, 62 years old. Anteroposterior and lateral views of lumbar spine. Increased osteolytic reaction is present in the body of the third lumbar vertebra, coinciding with the development of a sarcoma in a case of mixed osteolytic and osteoblastic Paget's disease.

by Homén⁶⁶ Schüller⁶⁷ described this condition antemortem in 1911 and correlated the bony deformity with central nervous system disturbances. Since that time a number of reports about this condition have appeared in the literature. A particularly detailed report relating this condition to Paget's disease in a single case is that of Wyck.⁶⁸

PATHOGENESIS. In Paget's disease when the bone becomes relatively malleable the weight of the skull upon the upright cervical spine causes a gradual collapse of the cranial base. The upper cervical vertebrae thereby press upon the posterior cranial fossa and upon the foramen magnum.

The round shape of the foramen magnum may change in this disease. Such deformity is particularly apt to occur at the ventral

portion of the foramen magnum. This deformity is actually a basilar invagination with upward displacement of the cervical spine in relation to the surrounding skull. It manifests an effect in three ways. The first is by pressure of the upper parts of the cervical spine against brain tissue of the posterior cranial fossa. The second is represented by a herniation of the cerebellar tissue and the brain stem into the cervical spinal canal. The third is a kinking of nerve tissue over the ventral invaginated rim of the foramen magnum as well as over the invaginated odontoid process.

CLINICAL SIGNS. Paget's disease shows frequent rather severe basilar impression. Yet paradoxically neurologic signs are less frequent in Paget's disease than in platybasia due to other causes. However symp-

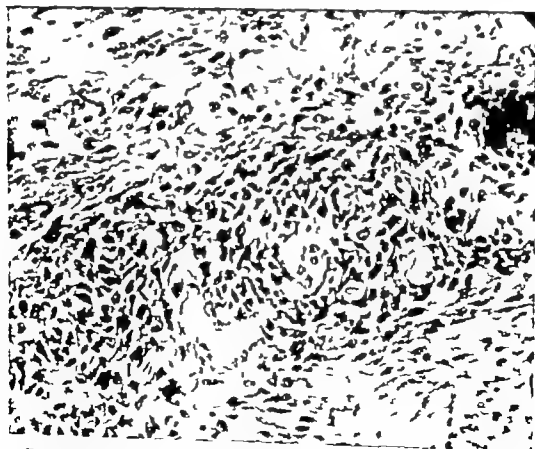


FIG. 310 Paget's disease with development of sarcoma. (Same patient as Fig. 309.) Note the large atypical cells and the immature osseous ground substance. Hematoxylin-eosin. High power.

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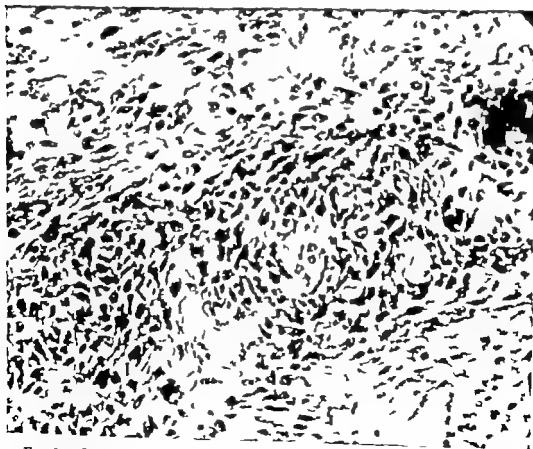


FIG. 310. Paget's disease with development of sarcoma. (Same patient as Fig. 309.) Note the large atypical cells and the immature osseous ground substance. Hematoxylin-eosin. High power.



FIG. 311 Paget's disease with development of sarcoma. (From Dr M. M. Pommeranz.) Anteroposterior and lateral views of both tibiae. A sarcoma has developed in a pre-existing area of Paget's disease in the proximal portion of the right tibia. The left tibia and the fibula show an osteolytic phase of Paget's disease.

toms have been described in this condition when it is caused by Paget's disease^{83, 84}. The symptoms and signs are primarily neurologic. These include ataxia from involvement of the posterior columns, pyramidal-tract signs such as hyperreflexia and the presence of pathologic Hoffmann and Babinski responses, and cerebellar signs especially dysmetria and dyskinesia. The cranial nerves of the posterior cranial fossa may be involved with motor paralysis⁸⁵.

In addition to the above findings of brain stem and cord origin, radicular findings from upper cervical segments may be noted. Such findings would include hyperesthesia and occipital headache in particular. If the deformity is severe enough, it is obvious that the vital centers of the medulla can become involved with a fatal outcome.

TREATMENT Surgical decompression is

indicated to alleviate neurologic symptoms if severe enough.

Malignancy in Paget's Disease. Throughout the literature are numerous references to malignancy developing in Paget's disease. The figures relating to incidence vary considerably. One must also consider that malignancy of bone is usually determined by the time death ensues. Paget's disease, however, may be overlooked in many cases. Moreover, since the cases with sarcomatous change usually become hospitalized, the hospital statistics will be weighted in favor of a malignant complication of Paget's disease.

There are figures reported in the literature indicating little or no incidence of malignancy in Paget's disease and figures that rise to as high as 15 per cent of incidence of malignancy.

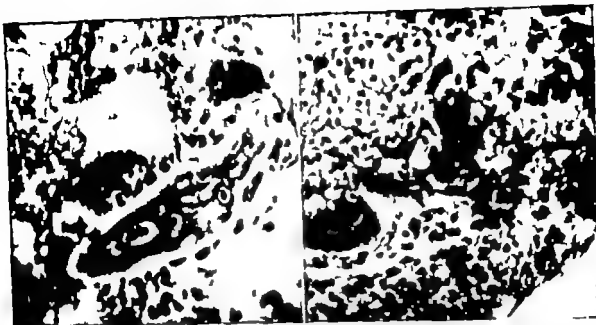


FIG 312 Sarcoma in Paget's disease (From Dr Charles H. Geschickter) Note large cells some showing mitotic figures. Areas of bone and cartilage formation of immature type are seen. Hematoxylin-eosin. ($\times 200$)

Schmorl found no sarcomata in 138 cases and in 116 cases Gutman and Kasabach⁷¹ found no malignancies. Dickson et al.,⁷² reported only 3 cases of sarcoma in 367 cases of Paget's disease at the Mayo Clinic. On the other hand Layan⁷³ indicated the incidence to be 8 per cent and the survival time to average 6 months after amputation. Lichtenstein⁷⁴ gave an estimate approximately as high as 15 per cent. It is also of interest that 5 of the 8 cases reported by Paget^{2, 27} including the initial case died of malignancy.

Schürch and Uehlinger⁷⁵ in a report of over 10,000 general autopsies found the incidence of malignancy in Paget's disease to be 0.6 per cent. The total number of cases of Paget's disease in the skeleton was not determined precisely. They concluded nevertheless that this percentage of malignancy was too small to designate osteitis deformans as a precancerous condition. This view is not held consistently in the literature.

Sugarbaker⁸ for instance indicated sar-

coma singly as well as in multiple foci. Brailsford⁷⁶ listed 6 cases of sarcoma in Paget's disease. Coley and Sharp⁷⁴ reported 72 cases of osteogenic sarcoma in persons over 50 years of age and in 20 of these a co-existing osteitis deformans was found.

The frequent association of sarcoma with Paget's disease leads one to the assumption that Paget's disease favors the development of sarcoma. Interestingly in 20 cases of Coley and Sharp⁷⁴ the sarcomata developed only in bones involved by the osteitis deformans. Gerstel and Janker⁷⁷ collected reports of 39 cases of osteogenic sarcoma in Paget's disease in which 11 cases showed sarcoma starting in different bones more or less simultaneously. This also occurred in 26 of 76 cases of sarcoma in Paget's disease collected by Summey and Pressly⁷ and in 10 cases described by Platt.⁷⁸

Even in cases in which sarcoma developed in various bones simultaneously, visceral metastases are usually absent. This has been the senior author's observation also. As Snapper²⁰ indicated this gives the idea

of multicentric origin of these bone tumors and militates against hematogenous dissemination

In the authors opinion since it is possible that some fault in tissue differentiation plays a part in the development of Paget's disease it is not unreasonable to assume that such a situation could be a precancerous condition. Further critical analysis of much of the literature suggests an incidence of sarcoma in Paget's disease beyond mathematical probability.

Sarcoma as found in association with Paget's disease as indicated above has some unusual aspects. They may be reviewed as follows:

- 1 It is usually an osteogenic sarcoma often with chondral, osteolytic or osteoblastic characteristics (Fig. 309). Lichtenstein⁷⁴ noted that the malignancies complicating Paget's disease of bone may not always be osteogenic sarcomas, they also may be fibrosarcomata and even malignant giant-cell tumors (Fig. 310).

- 2 These cases are progressively fatal but appear (Fig. 311) to be less rapidly fatal than the adolescent metaphyseal type of osteogenic sarcoma.

Two peculiar characteristics of this type of malignant degeneration are (a) a tendency for the tumor to spread by contiguity and often without distant visceral metastasis (Fig. 309) and (b) the frequent occurrence of the malignant change in more than one bone which may be separated as widely as a right humerus and a left femur (Fig. 312).

The reasons one must consider multicentric origins of these sarcomata in cases where more than one bone is found to be affected by a malignant lesion are:

- 1 The tumors may be found at widely separated areas yet absence of involvement of lung and other viscera and the blood vessels is against hematogenous spread.

- 2 On discovery the tumors may demonstrate the same degree of advancement, indicating simultaneous occurrence.

- 3 The tumors may show some differences in histologic characteristics.

SIGNS OF MALIGNANCY Contrary to the age group affected by the usual type of osteogenic sarcoma (23 years)⁷⁶ the group of Paget's-disease cases are found largely above the age of 50.

The malignant change is found in bone affected by the Paget's disease. It is also more apt to occur in those cases in which the osteolytic process predominates over the osteoblastic reaction.⁸¹

There is generally considerable increase in pain especially at night. The involved bone rapidly enlarges, and pathologic fracture is common.

Of interest is a case of the authors who suffered severe destruction of the lumbar spine by sarcoma. He first presented himself because of a fall due to partial paralysis secondary to tumor pressure upon spinal nerves (Fig. 309). Such cases are rare enough to merit very careful study in each instance. It is possible that blood studies, particularly alkaline phosphatase and sedimentation rate may show changes in serial determinations with the supervention of malignancy.

A case of the authors maintained a positive calcium and phosphorus balance until his death from a lesion involving most of the spine.

It should be emphasized that whenever undue bone pain occurs in a patient suffering from Paget's disease careful study even including planograms and biopsy ought to be considered.

Summary The reader cannot help but feel confused when confronted with such varied statistical data. Nevertheless there appears to be an incidence of malignant supervention in Paget's disease usually osteogenic sarcoma of varying histologic types.

The incidence of malignancy is higher in the older age group and in advanced polyostotic Paget's disease. Most of the statistical data do not take into account some of the following factors:

- 1 The duration of the Paget's disease in relation to the development of the malignancy.

- 2 The degree of dissemination of the



FIG 313 Paget's disease. White male 60 years old. The patient has widespread Paget's disease, including the skull. Anteroposterior and lateral views of right knee. The lower femur is the seat of advanced Paget's disease with osteoblastic reaction. In addition there is involvement of the patella by a similar but less advanced process. There is advanced hypertrophic osteoarthritis with severe narrowing of the knee joint and erosion and sclerosis of the tibial condyles. Similar changes occurred in other major joints of this patient.

Paget's disease and its relationship to the incidence of malignancy.

3 The chemical findings as reflected by alkaline phosphatase and sedimentation rate.

4 The true incidence of Paget's disease itself at all ages and stages which must be ascertained before the true relational significance of malignant supervention can be indicated.

5 The degree of osteolytic versus osteoblastic reaction. Very severe osteolytic reaction with exuberant osteoblastic response may be related to malignancy on the basis of cellular activity.

GENERAL COMPLICATIONS

Arthritis. In the authors' experience by hypertrophic osteoarthritis appears to be a

complication of Paget's disease. The reason is that the incidence and the severity of degenerative arthritis involving joints contiguous to Paget's-disease bone are out of proportion to the amount of change that is to be expected at any age group (Fig. 313). The implication of this observation is that patients with Paget's disease often will show symptomatology of advanced degenerative arthritis. Many times therefore symptoms in such patients are on the basis of joint origin not bone.

Cardiovascular Disease. This has been discussed in detail under etiology. Reiterating some of the thoughts contained therein, Paget's disease in itself presents certain characteristics that are an increased strain upon the cardiovascular apparatus. The more diffuse the Paget's-disease change

In the skeleton, the greater the circulatory load. This causes high cardiac output which represents a state of cardiac strain. Changes, therefore, can even induce cardiac failure.

The chest is deformed in advanced Paget's disease with elevation of ribs and considerable collapse of vertebral bodies producing severe kyphosis. This adds a mechanical strain to the pulmonary circulation and reduces respiratory excursions. In addition, there appears to be a generalized arteriosclerosis greater in degree than can be explained on the basis of age alone.

The pattern of circulatory disturbance induced by Paget's disease of bone is as follows:⁴¹

- 1 Increased pulse pressure
- 2 Increased cardiac output
- 3 Enlargement of the right auricle
- 4 Absence of significant anemia
- 5 Removal of these signs by application

of a tourniquet high on a markedly affected limb

- 6 The disturbance in the involved bone is felt to be compatible with multiple small arteriovenous aneurysms. The assumption is that the vascular bed of the affected bones acts as an arteriovenous shunt.

Hypercalcemia. Hypercalcemic symptoms will arise in Paget's disease upon immobilization by either prolonged bed rest or plaster fixation. It must be remembered that the primary process in this disease is osteolytic. An osteoblastic response occurs almost immediately. It is varied in degree under the most ideal circumstances. Most important in maintaining this so-called healing reaction is the stimulus of functional activity, weight bearing being the best example.

Immobilize a part—or even worse immobilize the entire patient—and an enormous osteoporosis results apparently due to a continued unchecked osteolytic process plus a diminution in the activity of the osteoblasts. When this occurs in a hyperemic bone structure, very rapid absorption of lime salts results.

The kidneys in the patients are usually aged older than their years. For Paget's disease infers some degree of premature aging. In addition, the kidneys are structures affected by arteriosclerotic changes. They often prove to be inadequate for the job of excreting the great excess of calcium and phosphorus. As a result, the levels of calcium in the blood increase markedly, producing symptoms of hypercalcemia.

Often when a major fracture occurs to a person suffering from Paget's disease, nausea, vomiting, abdominal pains, drowsiness, and even coma may ensue. In addition, pathologic calcification of various soft tissues including the kidney parenchyma may occur. Stone formation within the urinary tract also may result. It is vitally important to keep this serious, even fatal, potential complication in mind.

This problem must be anticipated at once on the occurrence of any fracture or any other condition requiring bed rest. So first one should avoid at all costs prolonged confinement in bed. Next, any fracture should be treated by that method allowing earliest ambulation or function of the part. In the long bones, this means internal fixation preferably of intramedullary type. In the hip, it infers a probable indication for prosthesis replacement. In the tibia, intramedullary nailing and/or walking plasters are indicated. In the flat bones and the spine, early ambulation with support and with sedation for pain should be the objective. Here it is better to accept a less perfect anatomic result.

Apophyseal separations, such as avulsion of the tibial tubercle, require open operation and fixation (Figs. 306, 318). This will be discussed further under surgery in the treatment of Paget's disease.

Walking plasters are also indicated in fractures of the legs (Figs. 265, 302). In the instance of the feet, where possible, steel plates in shoe soles are used to allow early weight bearing with relative comfort.

When patients are ambulated early, the diet should be high in protein and moder-

ately increased in calcium phosphorus and vitamin D. It also should be supplemented by androgens and estrogens. This too is discussed in detail under treatment.

During the period of enforced bed rest calcium and phosphorus intake must be reduced drastically. All milk and milk products, for instance, are forbidden. In addition magnesium carbonate must be administered preferably 4.0 Gm per day in divided doses. Androgens and estrogens are interdicted.

Mental Changes. In his original report Paget² emphasized the preservation of normal mentality in his patients. However, it frequently has been considered that skull changes and deformities might be responsible for mental changes. Snapper²⁰ quoted Schrijver and Stauder as stating that mental abnormalities, especially dementia praecox, occur frequently in Paget's disease. Stadler²¹ cited the case of three brothers with Paget's disease who showed mental as well as neurologic disturbances.

The authors have not observed gross mental aberration in any cases despite the opportunity of following many patients with advanced skull disease. It must be remembered that cerebral arteriosclerosis and mental deterioration on that basis may occur in Paget's-disease cases as a concomitant finding. The authors cannot corroborate that changes in Paget's skulls produce mental illness. It is true that deformity, such as compression of the foramina at the base of the skull, may produce local effect, but in general the inner table does not appear to enlarge greatly nor to become irregular. Furthermore, to the authors' knowledge, no proof of mental disease from skull pressure on the brain has been presented.

Chemical Changes. Numbers of data on Paget's disease have been accumulated by many workers, including the authors of this book. Certain specific findings have been ascertained and frequently confirmed. As yet, however, the factual information still does not clearly indicate the unknown cause of the disease.

Since the primary process of the disease appears to be osteolytic, one might assume that elevation of blood-serum calcium is present; however, this has not been observed. It is true that frequently it occurs when a patient with advanced disease is immobilized or becomes bed fast, but this is the result of excessive osteoporosis due to loss of functional stimulus to bone formation. When we consider chemical findings in this disease, we must consider both the degree of involvement and the stage of the disease.

Chemical studies of Paget's disease include routine laboratory blood-serum values and special studies. The routine blood-serum determinations are for serum calcium, phosphorus, alkaline phosphatase, and sedimentation rate (preferably Westergren).

Special studies include blood-serum magnesium and balance studies. The latter studies are of interest when they measure calcium, phosphorus, magnesium, and sulfur.

The senior author has amassed considerable data by balance studies, which were started with Laslo Hajdi at Johns Hopkins Hospital and continued with Corson White of Philadelphia.

BALANCE STUDIES. A balance study, as performed by the authors, is considered essential for a correct determination of the patient's metabolism of the studied elements, as well as essential for the determination of the indicated dose of magnesium to maintain a patient's calcium and phosphorus balance at an approximate equilibrium level.

The method of study is to give a diet containing approximately 0.3 Gm of calcium, 0.5 Gm of phosphorus, and 0.15 Gm of magnesium daily. The patient is on this diet for 1 week before a balance study is performed. At that time a rigid diet may be continued at home, with care to save all urine and feces and, of course, care to measure all ingested food. However, usually hospitalization is preferable for investigative work.

Diet consisting of 0.3 Gm of calcium

0.5 Gm. of phosphorus and 0.15 Gm. of magnesium

1 The stated mineral content of the majority of vegetables and meats varies greatly. Therefore it is necessary to list specific foods in order to obtain the desired gram molecular weight.

2 The following foods contain no trace of magnesium ^{22a}

Apricots dried
Blackberries (seeds removed)
Collards
Cottage cheese
Cucumbers (seeds removed)
Limas fresh
Parsley

3 The foods which contain calcium and phosphorus in greatest abundance are milk and eggs. They are excellent sources of these two elements, but both are poor in magnesium. Muscle meats are rich in phosphorus but their calcium content is low. Beans are fairly rich in calcium phosphorus and magnesium and serve as excellent sources of these elements. Wheat is poor in calcium but serves as an important source of phosphorus. Nuts and green vegetables such as broccoli, kale and celery are good sources of calcium ^{22a}

Diet Prescription 0.3 Gm. of calcium 0.5 Gm. of phosphorus and 0.15 Gm. of magnesium.

Breakfast

Fruit serving (orange juice)—0.030 Gm. of calcium 0.019 Gm. of phosphorus, 0.010 Gm. of magnesium
Cereal (refined)—100 Gm.—0.001 Gm. of calcium 0.011 Gm. of phosphorus
Cream (20%)—90 Gm.—0.037 Gm. of calcium 0.069 Gm. of phosphorus, 0.001 Gm. of magnesium
Total—0.118 Gm. of calcium, 0.099 Gm. of phosphorus 0.011 Gm. of magnesium

Lunch

Lettuce (1/2 head)—0.054 Gm. of calcium 0.031 Gm. of Phosphorus 0.011 Gm. of magnesium
Beets—100 Gm.—0.026 Gm. of calcium 0.039 Gm. of phosphorus 0.023 Gm. of magnesium

String beans—100 Gm.—0.065 Gm. of calcium 0.044 Gm. of phosphorus, 0.026 Gm. of magnesium

Total—0.145 Gm. of calcium 0.114 Gm. of phosphorus 0.060 Gm. of magnesium

Dinner

Chicken—80 Gm.—0.016 Gm. of calcium, 0.218 Gm. of phosphorus 0.027 Gm. of magnesium

Asparagus—100 Gm.—0.021 Gm. of calcium 0.052 Gm. of phosphorus, 0.012 Gm. of magnesium

Carrots—100 Gm.—0.042 Gm. of calcium, 0.040 Gm. of phosphorus 0.017 Gm. of magnesium

Potato—100 Gm.—0.011 Gm. of calcium, 0.056 Gm. of phosphorus 0.027 Gm. of magnesium

Total—0.090 Gm. of calcium, 0.366 Gm. of phosphorus, 0.083 Gm. of magnesium

At the start of the test, 5 Gm. of carmine is given to mark the stool. The urine beginning after the morning's first specimen is passed is collected for each 24-hour period. A creatinine test should be done upon the urine in order to be sure that each specimen represents a 24-hour aliquot.

Two identical separate portions of food are made up for each meal. These are then weighed. One of these portions the patient ingests. Care is taken to reproduce in the second portion the appearance and the amount of the first sample that is left on the dishes and the silverware by the patient. The same amount of material the patient ingests is collected therefore for analysis from the second sample. Further check for accuracy is done by weighing the residue of the portion served to the patient. In other words every precaution is taken to equilibrate the food sample analyzed with that ingested by the patient. Sample diets are used because tabulated diet values as far as far as minerals are concerned vary with the locality in which the food is produced.

The total food for a 5-day period is lumped and analyzed as a single specimen for phosphorus calcium, magnesium and sulfur.

The total stool should be saved for 5 days. This includes the stool first stained

with the carmine and stops with the collection of a second stool again stained with carmine which is given on the night of the fifth day.

The problem of the urine is simpler. Each day a specimen is agitated and a proportionate sample taken. This is lumped with samples proportionate to the day's total output of each of the other four days. For example if 2,000 cc. of urine is excreted by the patient on the first day 200 cc. may be preserved from this total amount for analysis. On the second day if 1,500 cc. is excreted 150 cc. will be preserved for analysis and so forth so that one tenth of each of the remaining three days' output of urine will be saved. Creatinine tests are done on the total urine output of each day to be sure that they are consistent in value and indicate that the urine represents a true 24 hour aliquot.

Five more days are allowed to pass which means 10 days from the start of the first period. On the sixth day (11 days after the start of the first period) carmine is again given to stain the stool and to mark the beginning of a second balance period. At this time the diet is maintained precisely as in the first period with care to measure it and analyze the food as well as the output of urine and feces. But in addition 4 Gm. of magnesium carbonate daily is given. The same method of analysis is carried out. One is then able to interpolate how much magnesium is required to maintain a patient in approximate balance as regards calcium and phosphorus.

For simplicity in correlating chemical facts with a particular phase of Paget's disease it is well to recall these 4 stages:

- 1 Primarily a monostotic form in which a single bone is involved is present. Here the blood-serum calcium phosphorus and magnesium are normal. The alkaline phosphatase is rarely elevated to any appreciable degree. The sedimentation rate is usually within normal ranges.

Elevation may occur in uric acid, urea nitrogen, blood sugar and cholesterol. These

variations do not occur in most cases of this phase of the disease and when observed are probably purely coincidental.

Balance studies demonstrate no appreciable loss of calcium phosphorus or magnesium but usually do show a loss of sulfur.

Such relatively normal findings in blood and on balance study are to be expected when this disease is not widespread or rapidly advancing. In this rarer form of Paget's disease there is no great activity.

- 2 Polyostotic forms with excessive evidence of the osteolytic phase will be reflected in the following chemical findings: normal calcium phosphorus and magnesium appear in the blood serum. The alkaline phosphatase will be found to be normal or slightly elevated. Not until considerable osteoblastic response occurs will this value rise. The sedimentation rate will be found to be uniformly elevated. Values above 40 (Westergren) are quite common.

The balance study will demonstrate a loss of calcium and phosphorus either a negative or a slightly positive balance of magnesium and a loss of sulfur.

- 3 Polyostotic forms with some healing reaction and with evidences of large areas of osteoporosis *circumscripta* in the skull or the pelvis in particular will be reflected in the following chemical findings: normal calcium phosphorus and magnesium values occur in the serum. Alkaline phosphatase is moderately elevated ranging from 20 to forty Bodansky units. Sedimentation rate is elevated values of 40 (Westergren) or above frequently being observed. The balance studies demonstrate moderate negative calcium and phosphorus balance and occasionally negative magnesium balance. Considerable negative balance of sulfur is found.

- 4 Advanced polyostotic Paget's disease with considerable osteolytic activity accompanied by marked osteoblastic response is the form usually observed and studied by most investigators. This is by far the commonest form. It represents advanced disease and is the result of progression of

the above phases over a period of years. The blood-serum values will be normal calcium, phosphorus and magnesium. Very high alkaline phosphatase levels are found. In fact these are the highest levels observed in any disease state. It is not uncommon to see values above 100 Bodansky units. The sedimentation rate again is elevated often well above 40 (Westergren). Often the elevation of sedimentation rate has been confusing to a clinician who may be following a patient who has had a coronary thrombosis and who also has Paget's disease. The sedimentation rate appears to be one of the most accurate determinants of activity of this disease. It probably reflects tissue breakdown whereas the alkaline phosphatase indicates unrequited osteoid and bone formation reaction.

Balance studies will consistently demonstrate definite positive balance of calcium and phosphorus, moderately positive balance of magnesium and loss of sulfur.

Therapy with large intakes of magnesium carbonate will lower this positive calcium and phosphorus balance to or near the point of equilibrium.

The consistent findings in well-developed Paget's disease are the loss of sulfur and the retention of phosphorus, calcium and magnesium. It is of interest that a loss of sulfur was the rule in all forms and degrees of Paget's-disease involvement. This finding was first observed and reported upon by DaCosta et al.²² and by Rabinowitch.²⁴ The precise significance of this finding is still not established. The most reasonable explanation is that there is total nitrogen loss as part of the tissue destruction of the osteolytic process.

BLOOD PICTURE. When a disease is as disseminated as is Paget's disease and when it may involve much of the flat bones and marrow structures, thoughts of aberration of the peripheral blood count and the marrow arise.

A consecutive series of 12 cases of advanced Paget's disease were studied carefully by means of peripheral blood counts

and iliac and pelvic marrow smears.²⁵ No aberration of the blood picture was determined.

TREATMENT

History of Treatment. The treatment of Paget's disease as of any disease of unknown etiology has been empirical. Isolated cures have been reported from therapies which differ widely both as to type and as to rationale. Prior to 1916 roentgen diagnosis was not well developed and unless there was a clinically advanced and typical case of Paget's disease little thought of the diagnosis of this disease arose. Even to this date many medical men consider the diagnosis of Paget's disease to be associated only with progressively increasing head size. After 1916 with the advent of more frequent roentgen studies many cases of Paget's disease were discovered and many reports have appeared in the literature since that time. It is now quite apparent that this disease occurs infrequently but that it is not rare.

It must be remembered that in the formulation of intelligent therapy for any condition it is of the utmost importance to diagnose the specific condition and to differentiate it from other conditions with which it might be confused.

It must be borne in mind that prior to 1930 many bone conditions probably were grouped much as the dermatologists grouped eczema because of the meager knowledge of the salient factors of these diseases. Therefore many modalities of treatment advocated prior to this time except for historical interest, would have no place in the present armamentarium. In fact many of the therapeutic regimens were used for what may not have been true Paget's disease.

So it has been important to determine not only what is Paget's disease but also what is not Paget's disease.

In 1908 Schirmer²⁶ carefully collected various measures of therapy and it is obvious that the treatments were merely empiric.

and unsatisfactory. The various types of treatment listed in his review were dietetic, antirheumatic, arsenicals, potassium iodide, phosphorus, massage, baths and electricity. The best recommendation was for mud baths which presumably gave some relief from pain. It was of interest that workers⁷ even used oophorectomy to reduce the endocrine effect although little of the gland's function was then known.

ANTISYPHILITIC TREATMENT

In the older days prior to 1910 those clinicians who thought that Paget's disease was of syphilitic origin were in the majority and they argued this as the cause and used antisymphilitic measures as the treatment. Lannelongue⁸ argued for syphilis as the cause of Paget's disease on either a congenital or an acquired basis. Fournier⁹ interpreted the disease as a retarded hereditary type of syphilis. Gaucher and Rostaine¹⁰ reported success in the treatment of Paget's disease from an antisymphilitic regimen especially in relation to improvement in walking in the first month after treatment but admittedly the result was poor thereafter.

Fortunately there were careful workers who both refuted and confused this theory. Parkes Weber¹¹ in 1908 did so on the basis of the age of patients with congenital syphilis in relation to the usual age of the Paget's-disease group. Furthermore he stressed the rare complaint of pain in congenital syphilis as contrasted with the violent pain common in Paget's disease. Finally he indicated no response in Paget's disease to antisymphilitic treatment whereas such treatment was of distinct benefit in the instance of syphilis.

Souques¹² then reported that only 5 of 14 cases showed a positive Wassermann and emphasized that the presence of a positive Wassermann reaction indicated the presence of syphilis but not the syphilitic origin of Paget's disease. Gaenslen¹³ in 1915 indicated that syphilis was not the cause as the blood Wassermann was proved negative in the great majority of his Paget's-disease cases.

In recent years it has become quite obvious that there is no possible correlation of syphilis to Paget's disease. If the former is present in a patient who has Paget's disease, antileptic treatment is of course indicated but no effect of such treatment on the Paget's disease occurs and none is expected.

ENDOCRINE TREATMENT

Hochelmer¹⁴ first used oöphorin, certainly a bold approach. It is of course doubtful if it was of any potency and certainly was not standardized. This produced no effect in Paget's disease so he then performed oöphorectomy with no better results.

Von Kutscha¹⁵ gave patients with this disease thyroldin on the presumption that it was caused by thyroid dysfunction. No beneficial effect was noted.

In 1930 Berman¹⁶ reported the use of adrenal cortical extract and calcium with improvement. This was based primarily upon relief of pain in 16 of 18 patients. It is of interest that cortical extracts at that date were of doubtful value. Kay¹⁷ in 1934 reported that 0.3 Gm. of suprarenal extract 3 times a day would ease the pain in Paget's disease. Watson¹⁸ in 1939 indicated that adrenal cortical preparations reduced serum-phosphatase levels and decreased pain. He used 1 cc. of Upjohn's Cortin each 2 to 4 days, then 5 cc. each 3 to 4 days.

Colt and Lyall¹⁹ reported excellent progress in a single patient who was given 5 to 10 units of parathyroid hormone daily with 2 Gm. of sodium acid phosphate 3 times daily. Their argument was that the fracture healed more readily although the general disease did not appear to be arrested in spite of the patient's claim of beneficial effect.

VITAMINS

Schneider and Widmann²⁰ after experimental endocrinologic studies in animals, studied carotene and vitamin A blood serum concentrations in several x-ray-confirmed cases of Paget's disease—6 cases in all. All cases studied showed low vitamin A levels, sometimes almost zero. Vitamin-C levels

were about normal in all cases. They concluded that the low vitamin A value in Paget's disease indicated a liver function disturbance producing an alteration of the vitamin A metabolism especially of the relationship between carotene and vitamin A. They felt they obtained improvement by administration of vitamin A after which serum-calcium levels were reduced from 14.56 to 12 mg per cent. [Authors Note: This is of questionable value in view of the fact that serum-calcium levels rarely if ever vary from normal in Paget's disease.]

Delmas-Marsalet⁹⁸ using calcium and vitamin D claimed improvement and reported lessening of pain and progress of skull deformity after 3 months of the above treatment. Nicory¹⁰⁰ used ultraviolet radiation and claimed improvement. Belden and Bernhelm¹⁰¹ used calcium lactate, viosterol and tomato juice with the digestive tract empty to favor absorption. They found that parathyroid extract aggravated the disease, which was contrary to Zimmer's³⁹ experience in 1930.

IRRADIATION

Radiotherapy was first discussed in 1908 in Schürmer's²⁴ review wherein it was stated that Schlesinger advocated such a regimen. Since that time radiotherapy has been used in many cases and reported on in the literature. Ledoux-Lebard¹⁰² reported relief in 7 cases which lasted for from 17 months to 2 years and at times slight recalcification could be demonstrated in afflicted parts. Several series of treatment were used.

Apparently the most successful effect of irradiation has been in the treatment of the actual areas of bone involvement and at least temporarily it has helped in relieving pain although no other measure of improvement can be determined.

The use of x-ray therapy upon the parathyroid glands in this disease however was reported by Merritt¹⁰³ on 3 cases in which he claimed the relief of pain. Actually he used it presumably on cystic lesions as well as in Paget's disease and one must

consider this number of cases too small to be significant.

MISCELLANEOUS

Taylor¹⁰⁴ reported relief of pain in a case by the use of cobra venom. John¹⁰⁵ in 1927 claimed striking improvement in 2 cases by a series of intravenous injections of 50 per cent dextrose solution each 2 days, starting with 20 cc. and increasing to 60 cc. No details were given as to total amount or duration of treatment.

BIOCHEMICAL AND SURGICAL

Historical Review of Surgical Treatment. In 1905¹⁰⁶ an early report on an osteotomy of the tibia resulting in a pseudarthrosis was made. In 1915 Gaenslen⁹² reported an osteotomy but no result was given.

In 1918 Abbe¹⁰⁷ reported admirable surgical correction of bone deformities. He observed 14 patients suffering from this disease. 4 showed changes in the jaw. In 2 of them surgical operations were done and excellent results obtained. In one an enormous regrowth of the alveolar roof and the restoration of the physiognomy of 20 years before resulted.

In 1930 Schnek¹⁰⁸ reported correction of malposition in Paget's disease by osteotomy and subcutaneous refracture after spontaneous fracture. The conclusion was that prompt healing resulted if sufficiently prolonged fixation was carried out.

Roberts¹⁰⁹ reported relief of pain by removing a 6 by 1 inch long strip from an involved area. Michaelis¹¹⁰ reported improved function and relief of pain by osteotomy. Except for the statement that bone fragments were joined with screws, his report was sketchy as to method.

In 1940 Brocq¹¹¹ reported osteotomy of the tibia which healed well. Haguenauf¹¹² reported successful laminectomy to relieve spine compression. In 1940 Henschen¹¹³ indicated laminectomy for compression plastic bone surgery for deformity, osteolysis and osteotomy for deformity, shorten-

ing for lengthened bones surgical removal of skull deformities and operative treatment for Paget's sarcoma. Careful evaluation of cases of the authors also indicates a definite place for surgery.

Historical Review of Biochemical Management. Examination of the literature has failed to reveal a group of cases in which there has been definite improvement in every instance. There has also been no evidence of sustained improvement based on chemical, radiologic, symptomatic and clinical signs.

The therapeutic agents used in treatment of this condition have been legion and beneficial results in isolated cases have been reported from methods diametrically opposed in principle. Parathyroidectomy, for example, was advocated by Ballin² and Morse, on the other hand Zimmer²⁰ also Van de Naele¹¹ used parathyroid hormone and Bernheim¹⁰¹ used a high calcium and viosterol diet. Coryn¹¹² used A T 10 (dihydrotachysterol).

Consideration of such apparent confusion in the treatment of Paget's disease leads to the thought that reports of improvement may have been chiefly remissions or psychogenic for in most of the cases attempted check on improvement was measured almost entirely by clinical chiefly symptomatic relief. Realizing that the disease has spontaneous remissions especially as regards objective and symptomatic manifestations after waiting for 22 years since their first case the authors have tried to establish a criterion of improvement other than relief of subjective symptoms so that improvement may be measured objectively. In addition the authors have worked with methods that may possibly work similarly to their own. Such a method is the use of aluminum acetate advocated by Helfet²⁰⁰ chiefly to nullify phosphorus absorption. Ghormley and Hinchey¹¹⁷ continued with this method and reported upon it.

It is important to state at the outset that the authors make no claim for cure of this disease. They do feel however that many

of their patients have been made more comfortable for sustained periods of time. Moreover biochemical and radiologic data indicate some improvement from the objective point of view.

The authors follow up of many cases covers a period of many years so that the possibility of remissions is not the only explanation. Even after 22 years of work by the senior author the basic scientific data in relation to bone metabolism in the normal and the Paget's-disease states are not yet sufficient to explain all the facets of the essentially empirical therapeutic program carried on by the authors. Nevertheless a regimen which has helped patients with this disease is presented so that it can be used critically by other workers in order to confirm or refute the findings of the authors.

The methods of treatment used by the authors vary moderately in relation to the predominant phase of the disease. The usual treatment involves administration of magnesium in the predominantly polyostotic osteoblastic phase of Paget's disease. In the authors' experience this is the most common phase and most cases eventually develop this form. Treatment also must include anticipation of the complications of the disease. Then such complications may be either avoided or treated.

One must remember also that when the factor that produces this disease is determined these methods may have to be re-evaluated.

Nevertheless the authors believe that in their therapeutic program lies a seed of truth which may prove to be a method of cutting the Gordian knot even though we do not know how to unravel it.

DaCosta et al.,¹ did basic work which identified the osteoblastic phase of this disease as one characterized by retention of phosphorus, calcium and magnesium. The authors' own studies performed in conjunction with Kafdl and Corson White corroborate DaCosta's findings.

Studies of x-rays and pathologic specimens further identified the osteoblastic

phase of Paget's disease. Obviously therefore, something that would reduce bone density might be of value as an agent for treatment of Paget's disease in its advanced forms.

The senior author referred to the use of magnesium and a low calcium and phosphorus intake for the treatment of Paget's disease in a review of bone metabolism which was presented before the American Orthopaedic Association in 1936 with A. Bruce Gill.¹¹⁸ Presented here is a more detailed outline of this regimen. It is possible that some prior reference to similar work has been overlooked; therefore, a description of the way this method came into being is presented.

In 1930 because of contact with Mitchell Rubin and the late David Shelling, both of whom at that time were in the Department of Pediatrics at Johns Hopkins Hospital, the senior author became interested in the study of mineral metabolism especially as it concerned the adult bony system. Association with these two workers continued for a number of years and many helpful suggestions were obtained.

The senior author learned from these men that Laslo Kajdi, also of the Department of Pediatrics at Johns Hopkins Hospital, had used magnesium as a decalcifying agent in a 6-year-old subject with marked diffuse hyperostosis. His use of magnesium was based upon the work in 1927 of Shelling Shipley and Holt,¹¹⁹ who had identified magnesium as a decalcifying agent.

Kajdi used a reduced calcium and phosphorus intake because magnesium carbonate, the ideal form of this mineral for this purpose, was a laxative. A large dose therefore could not be used without catharsis. By reducing the calcium and especially the phosphorus intake, the relative magnesium dose thereby could be increased.

Although Kajdi had used this regimen only in the aforementioned child, the senior author felt that the method might be of value in osteoblastic Paget's disease. The first case so treated was on the service of

A. Bruce Gill at the Philadelphia Orthopaedic Hospital in 1932. Within a few months, several other cases were treated with this regimen. Corson White's reports on the chemical studies in these patients indicated the following: serum calcium and phosphorus determinations were normal; alkaline phosphatase levels were elevated in these cases and balance studies showed retention of calcium, phosphorus and magnesium and loss of sulfur and nitrogen. After magnesium and the above regimen were given, the phosphatase levels declined, sedimentation rates fell, calcium and phosphorus excretion in feces and urine increased, magnesium retention was only slightly increased and sulfur loss was reduced. These patients were uniformly improved as regards subjective complaints; objectively they had more strength and tired less easily.

Deflection studies on involved bones under measured loads show increased flexibility of these bones within a few weeks after the institution of magnesium therapy.

Subsequent to this, the senior author continued his orthopedic work in Baltimore under George Bennett, with whose aid he saw a number of other patients with Paget's disease, one of whom supplied funds which permitted the setting up of extra technical work under Kajdi so that numerous balance studies could be carried out (Fig. 314). These balance studies and blood-serum studies as well as clinical follow-up were also most encouraging so that this regimen was adopted and has been followed through from that time until now. Many more cases of Paget's disease were seen and treated by the authors in the course of the next 21 years, the majority of whom have improved (Figs. 315). An application of chemical measures to this disease has enabled the authors to do surgery on numbers of cases with no untoward effects (Figs. 295, 306, 320).

Some cases, as a matter of fact, have had dramatic improvement by surgical procedures of marked deformities with no com-



FIG 314 Paget's disease. White female 70 years old. The patient was first seen and later followed by the senior author through the courtesy of Dr. George E. Bennett. The patient had widespread advanced Paget's disease. She was bedfast with severe pain in the left hip. The left lower extremity was maintained in nearly 90° of external rotation. Any effort at passive internal rotation from this position was both painful and impossible. (Reproduced from Gill, A. B. and Stein, I. J. *Bone & Joint Surg.* 18:949-951, 1936.)

(A *Left*) Anteroposterior view of pelvis. Pretreatment roentgenogram shows osteoblastic Paget's disease in the right ilium, the ischium, the ramus and the pubis. Osteolytic change is evident in the left hemipelvis. In addition, deformity of the left hip joint and the left upper femur as a result of Paget's disease is present. A severe hypertrophic arthritis of the left hip joint is present with practically total loss of the joint space. The arrow indicates a retouched bony spur driving from the ischium at the inferior aspect of the acetabulum.

(B *Right*) Anteroposterior view of pelvis. (Print is reversed.) Following a 6-weeks course of high-magnesium and low-calcium and low-phosphorus intake (4.0 Gm. of magnesium carbonate, 0.5 Gm. of calcium and 0.7 Gm. of phosphorus daily) the pelvis shows a reduction of excessive osteoblastic effect on the right side. There is some condensation of the ilium on the left giving a more uniform over-all pattern to the bone. The small exostosis arising from the left ischial ramus which is indicated in (A) has disappeared. In addition the left hip shows a much clearer joint space than in (A).

(C *Right*) Lateral views of left femur. Pretreatment roentgenogram on the left, post-treatment on the right. There is restoration of the medullary cavity after treatment, indicating a reduction of the endosteal proliferative reaction and the over-all osteoblastic reaction associated with the Paget's disease.

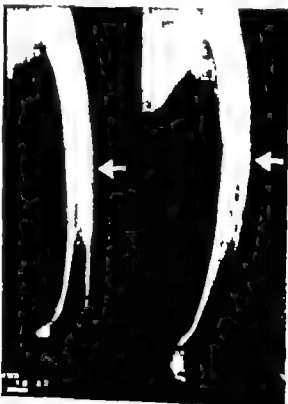




FIG. 315 Paget's disease. White female 42 years old Neck pain and stiffness, progressively increasing for 2 years The lateral cervical spine roentgenograms demonstrate the pathologic process most vividly and are used, therefore to illustrate the response of this patient to treatment. On an average daily intake of 250 mg. of calcium and 400 mg. of phosphorus, the urinary output per 24 hours was 190 mg. of calcium and 400 mg. of phosphorus. This represents a significant negative calcium and phosphorus balance and infers an osteolytic phase of Paget's disease.

(Continued on following page)

(A, *Top left*) Lateral view of cervical spine (October 1950) Osteolytic foci disease. This demonstrates almost complete loss of definition of the second, the third, the fourth and part of the fifth cervical bodies and their vertebral appendages. Additional views showed no encroachment upon the spinal canal. The patient was then placed upon a high-protein, high-calcium and high phosphorus intake plus androgen, estrogens and vitamin D. See text for details of regimen. 40 Gm of magnesium carbonate was given daily in divided doses 1 hour before meals. Neck brace applied because of fear of further collapse and paraplegia.

(B, *Top, right*) Lateral view of cervical spine. Eight weeks after beginning the calcifying regimen. There is already evidence of increased density in the involved second through fifth cervical vertebrae.

(C, *Bottom left*) Lateral view of cervical spine. Three months later and after 5 months of the calcifying regimen. Notice the further increase in ossification through the involved vertebral bodies and their posterior elements. The neck support was discontinued at night.

(D, *Bottom right*) Lateral view of cervical spine (December 1951). After 14 months on calcifying therapy, the trabecular detail in the involved area now compares favorably with that in the surrounding normal bones. The entire second through fifth vertebral area is fused into one solid bony mass. There are no intervertebral spaces. This fusion results from apposition of the bony margins of the vertebral bodies. This apposition occurs when the intervertebral disks totally herniate into the softened vertebral bodies. Compare with Figure 295. It is now obvious in retrospect, since greater bone detail is now present, that this process of disk prolapse and vertebral fusion had already taken place prior to (A). With ossification following treatment, the details of the fused mass are now apparent.

(E, *Bottom*) Cervical spine. Lateral views in extension and flexion (December 1951). Considerable movement occurs between the fifth, the sixth and the seventh cervical vertebrae as well as between the occiput, the atlas and the axis. There is no motion in the fused area between the second and the fifth cervical vertebrae. At this time these flexion and extension movements as well as rotation to 45° in either direction were obtained without any complaint. The patient had no symptoms. The brace was discarded. The calcifying regimen has been continued.





FIG 316 A Paget's disease. White female, 75 years old. The patient had been working actively as a domestic until she slipped and fell on a waxed floor. Anteroposterior and lateral views of right femur. Portable films showing short oblique fracture of the upper third of the femoral shaft. Note the enormous degree of density of the bone and the degree of obliteration of the marrow cavity.



FIG 316 B and C (Caption on facing page)

plications and no nonunions. Other cases even in aged individuals with severe disseminated Paget's disease have through the measures of internal fixation and early ambulation done well and developed no serious problems of hypercalcemia (a not uncommon phenomenon in such cases) (Figs 305-316).

The authors now do not do as many detailed complete balance studies as previously, feeling as they do on the basis of previous experience with balance studies that many of these cases can be handled empirically. However the ideal method of standardizing such a patient is still the utilization of complete balance studies. In the event that these cannot be done substitution through the use of various examinations of the blood serum plus modifications of the Sulkowitch test may be followed. This is particularly helpful in regard to the effect of magnesium because magnesium increases phosphorus and calcium outputting through both urine and feces but to a greater and relatively consistent degree through the urine.

Other workers have approached the biochemical management of Paget's disease through the use of other chemicals, a notable example being the work of Helfet¹¹⁰ on aluminum acetate which he used to reduce the phosphorus retention.

Chormley¹¹⁷ used a similar regimen. The particular mixture that he used is as follows: 5 fluidounces of Burrow's solution (aluminum acetate), 3 fluidounces of tolu balsam syrup and honey to make 16 fluidounces. *Directions:* 1 teaspoonful 3 times daily. In Chormley's report¹¹⁷ he felt that this mixture had some value. The role of aluminum in regard to the bone crystal and even to the bone formative or bone retractive stage itself is not a clear one except through its effect upon phosphorus absorption. Magnesium and strontium however both have other effects aside from those of reducing phosphorus absorption.

However recent work particularly upon magnesium and its role of adsorption upon the surface of the bone crystal¹¹⁸ and work indicating it is a local calcification blocking factor¹¹⁹ lead the authors to believe that it must play some role in the basic reactions of bone. Furthermore as proved by the authors numerous balance studies magnesium tends to reduce the retention of phosphorus and calcium in Paget's disease. The phosphorus retention is reduced chiefly in the bowel with its excretion in the feces and by some increased urinary excretion of magnesium phosphate. Calcium retention is reduced by the substitution of magnesium for calcium in the bone and by excretion of

FIG 316 B and C. (B *Left*) Anteroposterior and lateral views of right femur. Postoperative films following open reduction and introduction of the Rush femoral nail show satisfactory alignment. At operation the suspicion of marked osteoblastic Paget's disease with endosteal proliferation in particular was corroborated. The bone was so dense that it was difficult to ream a tract for the Rush nail with a motor-driven twist drill. The surgeon must be alert to this type of Paget's disease for a Küntscher type nail can become hopelessly entrapped in such osteoblastic endosteal bone. One must not drive a guide pin into such bone without previous reaming; for this type of bone acts as a compressible trap for anything driven in and not drilled in. In the authors' experience the Rush pin is indicated for this type of bone, and this illustration demonstrates its efficacy. Contrast this with Figure 305 where the medullary canal is enlarged and a large Küntscher nail or even two interlocking Küntscher nails may be required for alignment and fixation.

(C *Right*) Anteroposterior view of right femur six weeks after intramedullary fixation. There is considerable callus bridging the medial aspect of the fracture line and close approximation of the fracture. The patient was ambulatory with crutches beginning 1 week after surgery. She was encouraged to bear full weight upon this extremity 4 weeks after surgery. During this period of bedfastness she was on 4 Gm. of magnesium carbonate daily with low intake of calcium, phosphorus and vitamin D.

calcium in feces and urine as compounds other than phosphates.¹²²

Aspects of Biochemical and Surgical Treatment. There are four aspects to the treatment of Paget's disease: the first is to aid the healing of the osteolytic phase; the second is to handle the excess osteoblastic response; the third is to anticipate and to handle complications; the fourth is to correct deformity by the use of surgery.

The Osteolytic Phase. The primary lesion of this disease as stated previously is an osteolytic one. This usually is followed nearly simultaneously by healing response. Occasionally the osteolytic phase may persist. In this event a controlled calcifying regimen is indicated to obtain a healing response. It is imperative to do this because such softened bone deforms badly with complications that arise as a result of such deformation.

The authors use a regimen in the osteolytic phase of Paget's disease similar to that for postmenopausal and senile osteoporosis.

1 High-phosphorus high-calcium high-protein dietary intake is achieved by the use of (a) 1 quart of skim milk daily (b) generous servings of meat or fish 2 or even 3 times daily (c) 2 to 3 ounces of cottage cheese daily (d) 1 to 2 eggs daily and (e) green vegetables and fruit juices.

2 Vitamin D (a) 30 drops of Drisdol* without vitamin A (Winthrop-Stearns) should be added daily to the skim milk, which is to be finished on that day (b) For patients unable to tolerate milk, vitamin D is contained in 0.5 Gm. of dicalcium phosphate capsules or wafers which are taken as 1 to 2 capsules or wafers 3 times daily.

3 Combined estrogen-androgen therapy to minimize feminizing and masculinizing side effects.*

If the osteolytic process is very severe

* When the serum alkaline phosphatase is normal or only slightly elevated combined androgenic and estrogenic hormonal therapy is indicated. In the event that the alkaline phosphatase is high, there is adequate unrequited osteoid, so hormonal therapy is not indicated.

and if the patient is ambulatory initial large doses of testosterone may be given by injection. The regimen is to use 100 mg. daily for 3 days to a week and then to shift to oral medication for maintenance.

Maintenance dosage is testosterone 10 mg. daily combined with ethinyl estradiol 0.04 to 0.05 mg. (oral). Conjugated estrogen 1.25 mg. (Premarin® Ayerst) (oral) or estradiol 1.0 mg. (transmucosal) also may be used as the estrogenic component in conjunction with the testosterone.

4 If bone pain is a prominent symptom the addition of magnesium carbonate, 2 to 4 Gm. daily is indicated. This will not reduce the mineral absorption appreciably when a good level of intake as above is followed. It will however give some symptomatic relief.

The Osteoblastic Phase. This phase of Paget's disease is by far the most common one. Nearly all cases go on into this form. The overactive osteoblastic response is so great here that the original osteolytic phase is relatively overshadowed.

It appears that magnesium is most helpful in this stage. Its role in bone has been stated previously. The ideal method to determine the optimal magnesium dose is to do a balance study on both urine and feces. This method has been outlined clearly under chemistry. In addition blood-serum calcium, phosphorus, magnesium, urea, nitrogen, uric acid, alkaline phosphatase, sedimentation rate and cholesterol should be determined.

In the event that a complete balance study cannot be undertaken, then a diet of approximately 0.3 Gm. of calcium, 0.5 Gm. of phosphorus and 0.15 Gm. of magnesium is given. The patient should follow this diet for at least 1 week, then remain upon it until two 3-day studies of calcium, phosphorus and magnesium in urine are done. This will be essentially a low mineral diet such as that described by Bauer and Aub and modified by Albright and Reifenstein (see Part One p. 30).

The urinary calcium excretion upon such

a diet will be approximately 100 to 150 mg per day the phosphorus excretion approximately 175 to 225 mg per day and the magnesium output approximately 50 to 70 mg per day

In the osteolytic form of Paget's disease there is a tendency to retain phosphorus and calcium. As a result the output will be below the normal expected amount. This indicates a positive balance of calcium and phosphorus.

Magnesium therapy is given to promote increased fecal and urinary calcium and phosphorus excretion. The authors have developed an empirical formula in order to estimate the dosage of magnesium necessary to obtain a urinary excretion of 175 mg of phosphorus per 24 hours on a low mineral diet

$$4 a - b = x \quad c$$

a = excretion of phosphorus in milligrams per 24 hours on 4 Gm of magnesium carbonate (second balance period)

b = excretion of phosphorus in milligrams per 24 hours during basal study (first balance period)

c = 175 mg. — b i.e. added excretion of phosphorus to bring it up to optimal figure of 175 mg per 24 hours

x = dose of magnesium carbonate in Gm. per 24 hours to achieve this optimal effect

For example if the phosphorus excretion were 100 mg before magnesium administration and now is 150 mg on 4 Gm of magnesium daily interpolation indicates that the required magnesium dose would be 6 Gm. per day. The equation is

$$4 (150 - 100) = x (175 - 100)$$

$$4 \quad 50 = x \quad 75$$

$$50x = 300$$

$$x = 6$$

where

4 = 4 Gm of magnesium carbonate used in second balance period

50 = increased phosphorus excretion on 4 Gm of magnesium over basal or first balance period

x = dosage of magnesium carbonate in Gm per 24 hours to attain

ideal phosphorus excretion of 175 mg per 24 hours

75 = amount of increase of phosphorus excretion desired to attain ideal figure of 175 mg. per 24 hours

Patients requiring 6 Gm of magnesium carbonate or more to attain the ideal phosphorus excretion of 175 mg per 24 hours on this restricted test diet will require constant although less stringent reduction of phosphorus and calcium intake. Patients requiring from 4 to 6 Gm of magnesium carbonate for optimal effect are allowed to return to a relatively normal diet except for the restriction of milk and milk products.

Similar interpolation using calcium excretion figures may be done but this is not necessary if the proportion of intake of 5 to 3 of phosphorus and calcium is maintained and if the excretion is also in similar proportion.

Anticipation of Complications and/or the Treatment of These Complications If They Do Occur. Complications have been discussed in detail both the local and the general type. Important in treatment are the prevention of hypercalcemia and the prevention and the treatment of displaced fractures.

Rest of a part or bed rest of a patient with advanced Paget's disease in particular results in rapid osteoporosis of the skeleton. Particularly marked is the change in the bone areas involved by Paget's disease. This enormous calcium release into the blood may well produce hypercalcemia and all associated untoward symptoms and signs. It appears that the major bone-forming stimulus is weight bearing and stress upon bone substance by muscle action. Therefore any patient with this disease who becomes bedfast must be exercised as much as possible. If the recumbency is for systemic disease and is of prolonged duration every effort to exercise the patient within indicated limits must be followed. Here rigid dietary restriction of calcium and phosphorus intake is imperative. This infers absolute in

terdiction of milk and milk products such as cheese of vitamin D and of gonadal hormones (especially testosterone but also estrogens) In addition all proteins with particular emphasis upon meat and fish, should be maintained at no more than 1 Cm per kg per day Nuts, peas, beans, plums, apricots and peaches should be withheld as they have considerable phosphorus and calcium content.

In other words, the emphasis here is upon allowing carbohydrates and fats with minimum protein, gonadal hormone, vitamin D and mineral intake.

Diabetics will require modification of their insulin dosage to allow increased carbohydrates to replace protein.

In addition to those dietary restrictions listed above, magnesium carbonate in doses of 4 Gm or more each day, or magnesium chloride in doses of 3 to 5 Gm. a day, may be used. The latter is more cathartic than magnesium carbonate or lactate. Increased calcium diuresis on low-calcium intake will occur with magnesium carbonate or lactate and will be enhanced if 0.5 Gm of ammonium chloride 3 to 4 times daily is given.

Magnesium increases both calcium and phosphorus excretion, especially when the calcium intake is low.^{323, 325}

If the recumbency is the result of a fracture, all effort must be directed toward so treating this fracture, whether it is complete or incomplete, that early ambulation and if possible ambulation with weight bearing will be allowed.

Intramedullary fixation or walking plaster are methods of choice for such complications (Figs. 265, 305, 316).

The recent technique of intramedullary nailing have given the orthopedic surgeon a most useful tool in the treatment of fractures which complicate this disease (Figs. 305, 316).

Most disabling fractures in Paget's disease are of the long bones. These fractures are practically universally transverse. They are therefore ideal for intramedullary fixation (Figs. 305, 316, 317).

The bones may demonstrate considerable bow, however. Therefore a well fitting Kuntscher nail cannot always be used. Furthermore, the marrow cavity may vary from a very wide space to one that is completely filled in by dense endosteal bone formation. In either instance there are problems in regard to choosing and fitting a nail of proper type and size.

If the bow is not too great, one or two interlocked Kuntscher nails may well give excellent fixation. If the bow is considerable, a Kuntscher nail will perforate the cortex or even split it. In these instances the Rush nail, which is more malleable and which has a sled-runner point, will work better (Fig. 316). It may be necessary to use a single nail of this type or two nails. The authors have not had to use more than two nails in a shaft fracture in order to secure adequate three-point fixation.

In those rarer cases in which the marrow cavity is filled with dense endosteal bone, the central shaft may have to be drilled, and again a Rush type nail will be found to be best. Broaches to prepare track for a Kuntscher nail are not very satisfactory to ream this hard bone (Fig. 316). It is also helpful to reinforce the fracture site with bone allografts.

Dietary calcium and phosphorus and vitamin D restriction and the use of magnesium are also indicated here as outlined above until the patient becomes ambulatory.

When the patient is up and about, every effort to favor bone formation and calcification is indicated. This means the use of 100 mg of intramuscular testosterone daily for 1 week, then every other day for an additional week, then twice weekly for a third week, and thereafter 10 mg of testosterone each day orally until fracture healing has occurred.

At the same time 0.05 mg of ethinyl estradiol is given daily for 3 weeks out of 4. Vitamin D in the form of 30 drops of Drisdol® daily in 1 quart of milk and one of the potent multivitamin capsules a day are given as well. To the daily quart of milk

added 4 to 6 tablespoonfuls of powdered milk. Cheese, meat and seafood are urged with fruit juice to supply vitamin C to help osteoid formation. Magnesium is withheld.

This regimen is continued until healing of the fracture is accomplished. It is possible that temporary flare up of the rest of the Paget's disease may occur if it is the osteoblastic type. However, this must be borne with until the fracture is healed. When this occurs, the regimen indicated for the particular case of Paget's disease is re-instituted—that is, if it is of excess osteoblastic reaction, low calcium and phosphorus and high magnesium are used; if it is excessively osteolytic, the calcifying regimen is continued.

A calcifying regimen is important in the post fracture period. The authors have treated a fracture by intramedullary fixation with reduced intake of calcium, phosphorus and vitamin D and high magnesium intake. In this instance union did not occur in more than one year (Fig. 317). Cases similarly nailed with calcifying regimen have healed within 3 months (Figs. 305, 316).

The reason that most physicians have observed healing in fractures in Paget's disease is that the normal American diet actually has a rather adequate calcium, phosphorus and vitamin content. Even then, however, many observers know that fractures in this disease heal slowly on the usual diets and management of the fracture.

The authors also are working upon strontium as a possible further aid in speeding up fracture healing. This chemical has been advocated by Schorr¹²⁴ to speed the healing in postmenopausal osteoporosis; the authors have used it in treating postmenopausal osteoporosis with encouraging results. Studies on its use in fracture healing in normal and Paget's-disease cases are still being continued.

An interesting variant in Paget's disease is the avulsion fracture which may occur in several areas but is seen most commonly in the tibial tubercle. This is a favorite site



FIG. 317 Paget's disease. White female 78 years old. Anteroposterior and oblique views of right femur. These are 1 year following fracture and Kuntscher nail insertion. Excellent alignment is maintained. However, two factors may well be responsible for the delayed union here. The first is a mechanical one in that this patient had a very large medullary cavity and two interlocked Kuntscher nails undoubtedly would have given better fixation. The second is that this patient was maintained on a low intake of calcium, phosphorus and vitamin D with a high dosage of vitamin D. Since this case the authors no longer use such a postfracture regimen. (See text.) Note that ambulation and guarded weight bearing have maintained good bone density despite delayed union.

for the following reasons: the upper tibia frequently is involved and usually exhibits a severe osteolytic wedge at the anterior surface. The amount of stress sustained at the tibial tubercle surpasses that of any other tendinous attachment to bone. Avulsion does occur less often at the Achilles tendon insertion (another great stress point) because the calcaneus rarely is involved by

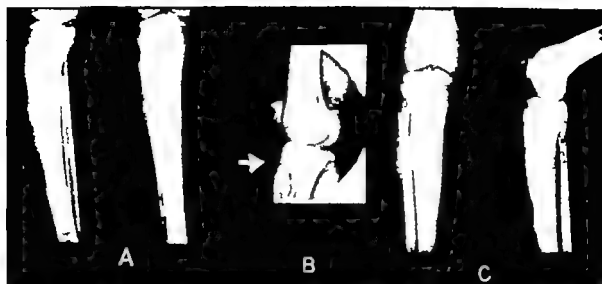


FIG 318 Paget's disease White male, 48 years old Anteroposterior and lateral views of tibia. (A) Osteoporosis circumscribed area in the upper tibia including the tibial tubercle which is the attachment of this patellar tendon. (B) Avulsion of the tibial tubercle after an ivory peg fixation attempt had failed Note the separation of the tibial tubercle as indicated by the arrow The patella is riding high. (C) Postoperative follow up roentgenograms 15 years after fixation of the patellar tendon in a tibial trough Braided silk suture material was used in this case. The technic is outlined in the text.

FIG 319 (Bottom) Paget's disease White female 50 years old. Anteroposterior and lateral views of tibia Marked compound anterolateral bowing deformity has occurred Bowing was so severe that the patient said it had been 10 years since she had seen her toes.



this disease however few cases of avulsion of the tendon of Achilles have been recorded. Rupture of the rotator cuff from the head of the humerus involved by Paget's disease theoretically may also occur so far no cases have been recorded to our knowledge.

It is interesting that in two of the senior author's cases avulsion of the tibial tubercle was the first sign of the disease. In one of his cases the tubercle was replaced with an ivory peg a year later the lesion recurred with little preceding trauma (Fig 318). A second case fixed with a long vitalium screw also pulled away this occurred several years later following some stress to the tubercle (Fig 306). These two cases have been followed for 5 and 15 years, respectively following a second repair using the authors' drill hole and suture technic. Two other cases have been treated in a similar fashion.

The method of fixation of the tibial tubercle is one in which multiple transverse drill holes are first made through the outer third

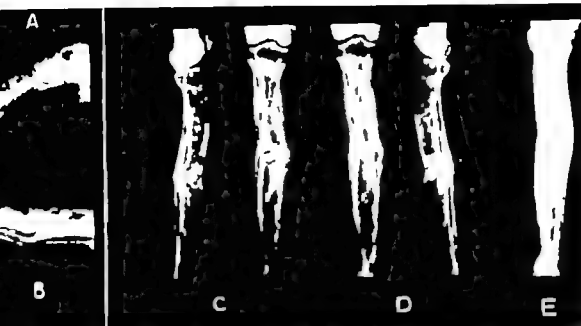


FIG. 320 Paget's disease (Same patient as Fig. 319) Delayed osteotomy was carried out to correct the tibial bow. (A) V-cut filled with bone chips. Note that the bow is still present. (B) Eight weeks later the fibula has been osteotomized subcutaneously at the level of the wedge cut in the tibia. Manual osteoclasis has been performed with resultant straightening of the bow. (C) Alignment and healing are good 3 months later. (D) and (E) Roentgenograms at 6 and 12 months postoperatively show good alignment and satisfactory union of the osteotomy sites.

of the crest of the tibia. The patellar tendon is then roughened and scarified on its under surface. The crest of the tibia is fashioned into a trough which receives the tendon. Suture material either silk or stainless-steel wire is threaded through the transverse drill holes and through the tendon (In one case heavy braided silk was used as the suture material in three others stainless-steel wire). This firmly anchors the tendon in the bone over a wide area. The extremity is immobilized with the knee extended for a period of 8 weeks. The results have been excellent; full function has returned in all instances. There have been no recurrences.

Bowing Deformity. Bowing of long bones is quite common and is unsightly and disabling (Fig. 319). The deformity results from healing of minute transverse fractures. The fractures usually produce severe bouts of pain. Many of these patients walk with the aid of crutches, not realizing that they

can be operated upon with reasonable assurance of success. Furthermore this bowing is self-perpetuating and aggravating. Since the stress is abnormal the bone is predisposed to additional fractures; hence the deformity persists and is even accentuated. The bone architecture therefore becomes more and more abnormal and the planes of the joints proximal and distal to the deformity lose their normal relation to each other.

Correction of the deformity might well be performed in the tibia which usually presents the most severe changes. The ideal operative procedure is a delayed osteotomy such as was suggested by Ferguson and which also has been described by J. R. Moore.¹²⁷

The procedure for the tibia is as follows: a crescent-shaped skin incision is made at the side of the deformity; the tibia is exposed and the periosteum is split and re-

flected. Then a wedge previously determined to correct the deformity, is removed. The wedge of bone is broken up and the bone chips are replaced in the defect in the tibia. The periosteum is carefully closed and the limb casted. Six weeks later an oste-

tomy of the fibula is carried out and the tibia is straightened, completing the osteotomy manually. The mass of bone chips placed subperiosteally acts as a ductile and malleable area lending itself to easy straightening (Fig 320).

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Inflammatory Reactions

SARCOIDOSIS

(See Boeck's sarcoid, benign lymphogranulomatosis, osteitis tuberculosa multiplex cystoides, Mortimer's malady, Schaumann's disease, maladie de Besnier, Boeck's uveoparotid fever or Heerfordt's disease, Hutchinson-Boeck's disease, benignes miliar-lupoid¹.)

Definition. Sarcoidosis is a chronic granulomatous condition which may affect any organ or tissue in the body and which presents noncaseating tubercles which otherwise appear markedly similar to those occurring in tuberculosis.²

Historical Notes. The first reference to the disease was made in 1889 by Besnier³ who described lupus pernio of the face. Following this in 1898 Hutchinson⁴ referred to Mortimer and described another form of lupus vulgaris that was nonulcerating and nonerythematous. In 1892 Tenneson⁵ also described a lupus pernio. In 1899 Boeck⁶ described a multiple benign sarcoid of the skin. He actually referred to a disseminated miliar sarcoid of the skin and because it had a microscopic similarity to sarcoma he named it a benign sarcoid. Darier and Roussy⁷ described a subcutaneous variety of a noncaseating sarcoid in the subcutaneous tissue.

The above descriptions were made by dermatologists whose recognition of the skin manifestations of this disease represented the first medical description of it.

In 1909 Heerfordt⁸ described a uveoparotid fever which presented an inflammation of the middle tract of the eye with associated parotid swelling and fever. He also noted that this syndrome included cerebral spinal complications, with paresis particularly of the seventh cranial nerve.

From the point of view of involvement of bone in 1919 Jüngling⁹ described a multiple cystic form of tuberculosis that occurred in bone. He did not clearly define it however and one cannot be certain whether the condition he described was truly tuberculosis in an aberrant form or Boeck's sarcoid.

In 1936 Schaumann¹⁰ analyzed the literature with regard to this unusual condition and tried to pull it together into a single systemic condition. He felt that there was a relationship between this condition and Hodgkin's disease and he named the entity benign lymphogranuloma. A summary in interpreting this as a systemic disease¹¹ described it as sarcoidosis or "Besnier-Boeck-Schaumann disease."

Etiology. Many observers have reported variants in regard to this condition. The etiology is not yet established clearly except that it is a granulomatous lesion. It has been considered by many to be noncaseating tuberculosis and there have been reports on the presence of tubercle bacilli in lesions of this condition.

However it is of interest that when this condition is widespread the reaction of the patient to a tuberculin test is either negative or very faintly positive. Furthermore if a patient with sarcoidosis develops true tuberculosis the lesions of the sarcoidosis disappear. Therefore it is held by some individuals that this might be an allergic response to tuberculosis. This is not altogether tenable however in view of the fact that the reaction to tuberculin when this condition is full blown is slight or even negative. Proof that the tubercle bacillus is the etiologic agent by fulfillment of Koch's postulates has never been presented.

In view of the very interesting finding of

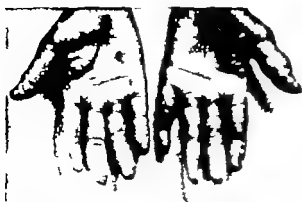


FIG 321 (*Left*) Sarcoidosis. (From Dr M M Pomeranz) Hands. There are nodular skin lesions with scaling. Note the annular constriction of the tip of the index finger right hand, and the tip of the little finger right hand. Further deformity is present in other fingers, particularly the interphalangeal joint of the left thumb.

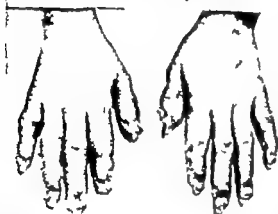


FIG 322 (*Bottom*) Sarcoidosis. (Figs. 322 to 325 from Dr M M Pomeranz) Both hands. Anteroposterior view (see Figure 321). Irregular areas of cancellous destruction are to be observed in the phalanges of the left fifth finger the distal portion of the proximal phalanx of the left index finger the tuft of the left thumb the middle phalanx of the right ring finger and the distal phalanx of the right fifth finger. Other less marked scattered changes are to be observed throughout the fingers.

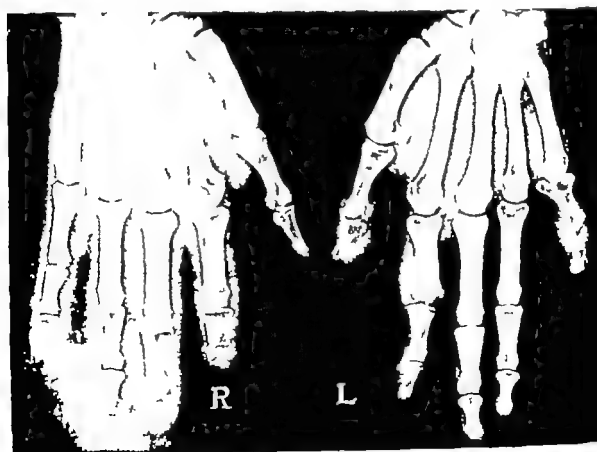




FIG 323 Sarcoidosis (Same patient as Fig 322) Anteroposterior view of right elbow and forearm Ovoid irregular areas of cancellous destruction are observed in the lower ulna and the radius and in the olecranon process



FIG 324 Sarcoidosis. (Same patient as Fig 322) Anteroposterior view of feet. Irregular areas of bone destruction to total involvement of the phalanges are observed scattered throughout both feet. The right fifth metatarsal shows very definite circumscribed areas of bone destruction with no appreciable periosteal reaction. The lesions appear "punched out."

negative or only slightly positive reaction to tuberculin in an age group where tuberculin tests usually are found to be positive one wonders whether or not this condition develops in individual who notably have an altered immune reaction to tuberculosis or to old tuberculin or whether for some strange reason a reversal occurs in which an individual may have been positive to tuberculin and then on developing sarcoidosis have become negative There is no proved situation to illustrate or document this thought however The converse is common and well known—that an individual with a negative tuberculin who has sarcoidosis will show a resolution of the sarcoid lesion and the development of a positive tuberculin with the development of tuberculosis

Varieties. There are many varieties of this particular condition and it is easy to understand how this would occur It is a chronic granulomatous disease which may involve any organ system or any structure The authors therefore are not surprised to find sarcoidosis of the following (1) skin (2) subcutaneous tissue (3) uveal tract of

the eye (4) lymph glands (5) lungs (Fig 325) (6) gastro-intestinal tract (7) salivary glands (8) endocrine glands giving rise to myxedema when the thyroid is involved or to pituitary change in involvement of that gland (9) kidneys with development of uremia (10) bones (Figs 321 to 324 326) (11) multiple groups of other tissues (tendons tendon sheaths voluntary muscles testes mucous membrane breasts) and (12) lacrimal and salivary glands (when these glands are involved by this condition it is referred to as Mikulicz syndrome)

Clinical Features. Many patients have no symptoms A diagnosis in these cases may



The bone lesions require no treatment but frequently biopsies are made for diagnostic purposes.

Prognosis. The prognosis is fair to good depending on the areas involved and the degree to which they are involved.

FIG 327 Infantile cortical hyperostosis (Caffey) (Figs. 327 to 330 from Dr. Herman W. Ostrum) Colored female 5 months old. The patient was admitted with a history of 1 day's swelling and pain in the left leg. The mother was alert to the possibility of this disease as a sister of the patient had been seen 3 years earlier with the same entity.

Anteroposterior view of upper extremities (June 5 1953). There is bilateral periosteal proliferation and cortical condensation involving both humeri radii and ulnae. There is also soft tissue swelling of the arms and the forearms.



FIG 328 Infantile cortical hyperostosis (Caffey) Anteroposterior and lateral views of low involvement is in both tibiae. Periosteal proliferation is present on the anteromedial aspect of the tibiae.

(Same patient June 5 1953) Anteroposterior view of the arms.

(Same patient June 5 1953) Anteroposterior view of the arms.



FIG 329. Infantile cortical hyperostosis (Caffey) (Same patient as Fig. 327.) Anteroposterior view of upper extremities (July 27, 1953). The periosteal reaction noted 6 weeks earlier is resolving, but cortical thickening is still present in the long bones.

Death usually is more apt to occur from complications rather than as a specific result of the disease itself. It is basically a benign condition but the processes that characterize it can affect the body in a widespread manner and if they happen to strike vital areas they can cause serious problems to the patient and even a fatal outcome.

INFANTILE CORTICAL HYPEROSTOSIS (Caffey's Disease)

Definition. This obscure idiopathic disease affects infants under the age of 6 months. It is characterized by subperiosteal new bone formation on the shafts of long bones and of the mandible by swellings of the overlying soft tissues and by hyperirritability (Figs. 327 to 330).

Historical Notes. Roske¹ presented a case



FIG 330. Infantile cortical hyperostosis (Caffey) (Same patient as Fig. 327.) Anteroposterior view of lower extremities (July 27, 1953). The periostitis has disappeared entirely on the right tibia and is resolving on the left tibia. There is definite cortical thickening of the left tibia. This too eventually resolves without deformity.

In 1930. However, it was 1939 before another case was reported this time by Caffey² who included it in a paper on skeletal manifestations of syphilis in infancy. A clearer delineation of this syndrome occurred when Caffey and Silverman³ included this case with three more in 1945. Since then additional case reports have

appeared and attempts have been made without success to determine the precise cause.

Etiology The etiology of this disease is unknown. It has been confused by some individuals with hypervitaminosis A but it definitely is an entity distinct from this condition (Fig 246).

Virus agents have been suspected but never proved to be a cause. It is of interest, however, that Caffey's conclusions are that infantile cortical hyperostosis still may be an infectious process. This is based on the fact that it is associated usually with fever, increased sedimentation rate, and such other features as pallor, painful pseudo-paralysis and pleurisy.

However, against the hypothesis of infection are the facts that serologic tests for bacterial and viral agents have been uniformly negative. Cultures by various methods also have proved to be sterile.

Clinical Features. The earliest signs are soft tissue swelling over the long bones or the mandibular region in association with which there is definite irritability and peevishness. The soft-tissue swellings are sudden in onset. They present wooden in duration and appear to be located beneath the subcutaneous fat in the muscular planes. These soft tissue changes precede roentgenographic evidence of bone changes and are subsiding and no longer tender by the time that the x-ray changes are observed (Figs 327 to 330).

Remissions, relapses and protracted duration of the disease comprise the usual pattern.

Lymphadenopathy is usually not associated.

X RAY FINDINGS It must be recalled that the roentgenographic bone changes follow the soft tissue swellings. The x ray changes actually occur at the times when these swellings are receding. These changes have been observed in all tubular bones of the skeleton (Figs 327 to 330). The flat bones commonly involved are the mandible and the scapula.

Caffey indicates that the scapular lesions always have been unilateral and always have been noted during the first 8 months of life. Similarly, mandibular lesions are not noted in older infants or children. Clavicular lesions are found at all ages and may be either unilateral or bilateral.⁴

A peculiar lesion has been found in the lateral arcs of the ribs, a so-called "costal hyperostosis." In infants this may be associated with pleural effusion.

The pelvic bones and the vertebral column have not been involved. Epiphyseal ossification centers and epiphyseal plates appear normal.

The involved bone or bones show marked proliferative reaction. This begins subperiosteally and may vary in degree from a small portion of the length of the bone to the entire length of the bone (Figs. 327, 328). This reaction may be either smooth or quite irregular. Advanced changes are a blending of the subperiosteal proliferative bone and the enlarged cortex into an expanded, thickened over-all bone structure which shows some osteoporosis (Figs 329, 330).

With healing there appears to be osteoclasia as a part of a gradual modeling process so that eventually normal bone structure and outline are restored completely.⁵

LABORATORY FINDINGS. Increased sedimentation rate, leukocytosis and increased alkaline phosphatase usually are noted. Anemia has been noted severe enough at times to require transfusion.

As stated above, various studies searching for infectious regions have proved to be negative.

Pathology In so far as the authors know there are no detailed autopsy reports on this disease. Biopsy specimens, however, have shown periosteal edema and thickening associated with subperiosteal new-bone formation. Occasional examples have shown edema in muscle tissue along with fibrosis and some necrosis. There is no evidence in either bone or soft tissues of hemorrhagic or inflammatory reactions.

Differential Diagnosis. Caffey's disease must be differentiated from syphilis of bone with its associated considerable periosteal reaction observed particularly in the shins.

Hypervitaminosis A has not been seen in persons under 12 months of age and is not associated with mandibular thickening. No fever is observed in hypervitaminosis A (Fig 246).

Scurvy in severe form will produce considerable periosteal proliferative reaction, but this of course shows additional roentgenologic signs on the basis of the typical scurvy lines and other typical radiologic appearances of scurvy (Figs. 239 to 245). Furthermore scurvy is not seen at that age. Fever is observed in scurvy.

Osteomyelitis is usually less widespread and associated with considerable bone reaction.

Malignant tumors can be differentiated

primarily on the type of changes in the bone and upon possible changes of the viscera.

Finally the disease must be differentiated from Engelmann's disease which is characterized by progressive diaphyseal dysplasia. The variation here is that this disease primarily involves the long bones of older children. The major radiologic effect is observed in the medullary portion of the bone rather than the cortex and the periosteum alone. Sclerosis occurs in both the medullary and the cortical zones. There is therefore a fusiform bony enlargement which never shows as a separate layer of subperiosteal new bone.⁶

Treatment. No treatment is known except supportive. The disease appears to be self limited and antibiotics and chemotherapeutic agents have been reported to be ineffective.

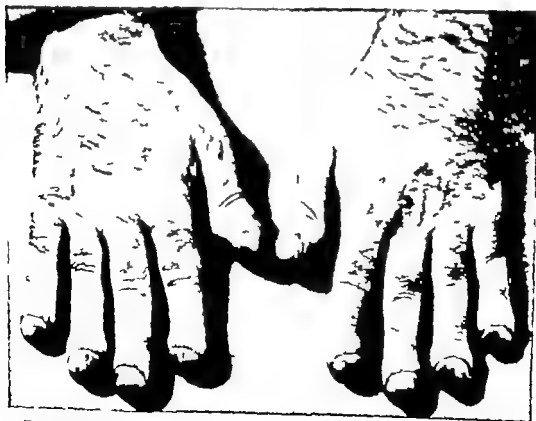


FIG. 331. Pulmonary hypertrophic osteoarthropathy (Figs. 331-332 from Dr. M. M. Pomeroy). Hands. Rounding of the nails and clubbing of the distal ends of the fingers are present.



FIG. 332 Pulmonary hypertrophic osteoarthropathy (Same patient as Fig 331) Feet. Clubbing of the distal ends of the digits is present

Prognosis. In general recovery begins within a few weeks to a month after the onset of the disease and usually eventuates in complete recovery within a period that



FIG. 333 Pulmonary hypertrophic osteoarthropathy (From Dr M M Pomeranz) White male 30 years old Anteroposterior view of both feet. It can be seen that there is hypertrophy of the tufts. This condition therefore involves not only the soft tissues but also the bony structures.

averages around 8 months from the onset of the disease. It has been observed however to last for as long as 2 years.⁴

PULMONARY HYPERTROPHIC OSTEOARTHROPATHY

Definition. This disease is a condition manifested by clubbing of the fingers and periosteal thickening of the long bones particularly of the hands and the feet and frequently is associated with polyarthritis of both the extremities and the spine joints (Figs. 331 to 334). It should be differentiated from a minor degree of clubbing of the fingers which is associated only with soft tissue enlargement without bone change. It was first described by Pierre Marie.¹ Hamberger also described it.

Etiology. The commonest causes are congenital heart disease with cyanosis and bronchiectasis. It also is seen not infrequently with cancer of the lungs, lung abscess, empyema, tuberculosis and pleural or mediastinal malignancy. Sometimes it may occur in association with an osteogenic sar-



FIG. 334 Pulmonary hypertrophic osteoarthropathy (From Dr M M Pomeranz) Anteroposterior view of both lower legs. Changes in the tibiae are those of a periostitis. These changes are nonspecific and are best observed in this case at the medial borders of the lower thirds of the tibiae.

coma and sometimes these changes may antedate radiographic evidences of metastases to the chest.

An additional variety of causes have been adduced but they are associated only with soft tissue clubbing and not the full picture of polyarthritis with periosteal thickening. Even a familial type has been described.²

Clinical Features. There is a gradually progressive clubbing of the fingers (Fig. 331). The skin of the distal portions of the extremities shows some thickening also. In advanced cases, the long bones may show relatively generalized periosteal thickening which may be palpable (Fig. 334).

Polyarthritis of both the extremities and the spine may produce pain, swelling and restriction of motion.

Occasionally periosteal thickening only of bones and no other clinical findings may occur. This is a much rarer situation however it would be evident only roentgenographically.

LABORATORY FINDINGS. There are no diagnostic laboratory findings except in association with the primary causes.

X-RAY FINDINGS. A layer of new bone under the periosteum extending along the shaft is observed (Fig. 334). This condition is usually symmetrical. This periostitis is not sun ray but rather onion peel. It is layered in a longitudinal direction. It should be looked for most commonly in the phalanges, the metacarpals and the metatarsals. The long bones are involved but to a less frequent degree. The skull and the carpal and the tarsal bones usually are not involved. The terminal phalanges show thickening of the tufts with associated soft tissue swelling of the tips (Figs. 331 to 333).

Pathology. The basic pathology is essentially subperiosteal new bone formation and this new bone may actually remain separate or may fuse. Those joints which are involved frequently show synovial thickening.

Treatment. The underlying disease is the problem. The bone changes are actually

only symptoms of the disease. It is interesting that in those cases in which these changes are found in congenital heart disease improvement of the cyanosis by modern surgical techniques results in partial or complete disappearance of bone and joint lesions.

Similarly following lobectomy or pneumonectomy for bronchiectasis bone and joint changes also remit.

Prognosis. The prognosis is that of the basic underlying condition.

GOUT

Definition. Gout is a constitutional and oftentimes hereditary disease characterized by a disturbance of purine metabolism. The disturbed metabolism may be manifested by various effects ranging from renal colic to single or multiple arthritis, bursitis or tendinitis.

Historical Notes. Gout was described by Hippocrates in the big toe, the wrist and the knee. Sydenham wrote on the clinical aspects of this disease with which he was afflicted. The name gout¹ arose in the thirteenth century from the French word *goutte* meaning a drop. The condition was likened to the effects produced by a poison entering the joint drop by drop.

In 1797 Wollaston² demonstrated that tophaceous deposits were composed of sodium urate crystals.

Colchicine was used in the treatment of this disease as early as the fifth century³ by Byzantine physicians. It was introduced into Europe in 1763 by Von Stork. Later on treatment involved the use of a low meat intake, temperance, bleeding and purging with colchicine.¹¹

In 1847 the disease was associated with an elevated blood uric acid.⁴ Following this, there was really no great advance in either the understanding or the treatment of this disease until very recently.

For the past century methods and drugs known then with few exceptions have been the chief standby. Cinchophen and its de-



FIG. 335 (Top) Gout. White male, aged 40 years in 1940. This series of roentgenograms goes from 1940 to 1952 in a case of severe chronic tophaceous gout of familial type. Anteroposterior view of both feet (1940). The print is reversed. Early tophaceous deposits and erosions are seen on the inner side of the right naviculo-cuneiform and the cuneiform first metatarsal joints.

FIG. 336 (Bottom) Gout. (Same patient as FIG. 335) Anteroposterior and lateral views of both feet (1942). The prints are reversed. Tophaceous deposits again are noted, this time in association with joint changes, on the inner border of the right foot. Note the early cystic lesion of the medial side of the distal end of the left first metatarsal. Spur formation and early cystic changes are seen in the midtarsal areas bilaterally.



rivatives have not proved to be too popular because of their toxicity. Salicylates a discovery of the latter nineteenth century proved to be remarkably efficient in helping to control levels of uric acid and to aid the body to excrete this material. More recently ACTH and cortisone with their effect have highlighted future research potential.

Incidence. Clinical manifestations of gout may occur in any race or sex. Primarily the condition is found in white males after the third decade of life. Earlier derangement of blood uric acid levels may be observed but usually without clinical symptoms and signs.

It is apparent that the tendency toward this disease is often hereditary (Figs. 335 to 338). Many members of a family may show all of its characteristic manifestations.



FIG. 337 Gout. (Same patient as Fig. 335.) Anteroposterior and lateral views of both feet (1947). The destructive areas in the head of the left first metatarsal and the base of the proximal phalanx have progressed. On the right side a cystic area is seen in the base of the fourth metatarsal. Metatarsal arthritis is seen bilaterally more severely on the right. The tophaceous material is calcified in the right tarsal area.



FIG. 338 Gout. (Same patient as Fig. 335.) Anteroposterior and lateral views of both feet (1950). Note the progression of the lesions observed in the previous illustrations.

other members of the family may show simply elevated serum uric acid

Etiology Gout is due to a metabolic defect involving uric acid metabolism. Bauer has described three enigmas of this disease (1) elevated serum uric acid (2) abnormal excretion of urate and (3) deposition of urate in the tissues.⁸ Elevation of the serum uric acid is a relatively constant finding both in people who are susceptible to developing acute gout and in those who are afflicted with chronic tophaceous gout. In people who are in acute gouty attacks however, the degree of elevation of uric acid cannot be considered to be a consistent laboratory method to predict an attack or to determine the severity of an attack.

In any event it has been shown clearly that the serum uric-acid level is more important than the whole blood uric acid.⁹

It is important to consider that the uric acid level may arise in cases of renal impairment, in eclampsia in leukemia in polycythemia vera and in hemolytic states

Therefore such conditions should be ruled out before much significance is related to the uric-acid finding

At one time it was considered that gout was due chiefly to elevation of uric acid levels because of renal retention. Now however evidence indicates that the elevation of uric acid results from increased uric acid formation

Of interest is the fact that colchicine can almost miraculously terminate an acute attack of gouty arthritis and yet will not affect the serum uric-acid level and vice versa. Probenecid (Benemid®) which can cause the fall of the uric-acid level, produces little effect upon the acute arthritic manifestations

Therefore although the uric-acid level is extremely important in establishing the diagnosis of gout, the final development of gouty manifestations in the joints and the soft tissues appears to be associated with some as yet unknown factor. Microscopic sections show no tophaceous material in



FIG. 339 Gout. White male 56 years old. Severe gout with wide spread tophaceous deposits even in the renal pelvis. Lateral views of both elbows. The tophaceous deposit in the right olecranon bursa is slightly calcified. It has eroded into and destroyed the adjacent portion of the olecranon process.

acute gout. Later accumulations will occur. The soft tissue joint reaction may result from defects associated with excretion of uric acid and in the long standing forms sufficient changes in joints and soft tissues will have occurred to allow a predisposition for the salts of uric acid to be deposited as massive tophi in involved tissue (Figs. 337 to 349).

Recent investigation into uric-acid metabolism involves the use of nitrogen 15 to tag synthetic uric acid and to follow its behavior in the body. This work has been done simultaneously by C. B. Brown, J. H. Talbott and DeWitt Stetten. The work of these investigators has been directed at studying normal metabolic processes leading to uric-acid formation and abnormal metabolic processes as well.

When a small amount of nitrogen 15 uric acid is injected intravenously the miscible pool is determined. The miscible pool of uric acid is defined by Stetten⁷ as

that quantity of uric acid present in the body

in a condition capable of prompt mixing with injected uric acid. This quantity is of the order of 1 gram of uric acid in normal man where it may be supposed to include all the uric acid in the body. It is increased in the gouty individual to two grams or more even to values as high as thirty grams having been recorded.

The miscible pool of uric acid is also that amount of uric acid which is dissolved in the body fluid. Stetten describes one sixth as being in plasma water and five sixths in extravascular water but further than that actually the urate in tophi also must be considered to be part of this pool. Solutions of uric acid are miscible with the surfaces of tophi; this corresponds to Stetten's consideration that there may be continuous precipitation and solution of tophaceous urate. The kidneys remain the major point for excretion of uric acid and certain drugs are particularly effective in stimulating urinary excretion of uric acid. These drugs are known as uricosuric drugs. They are represented by materials such as probenecid

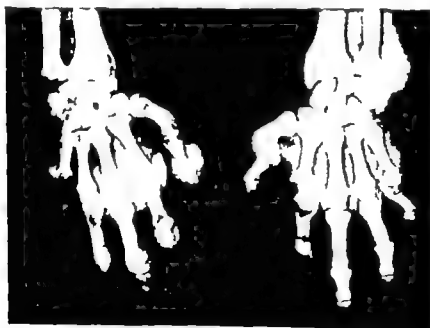


FIG. 340 Gout. Anteroposterior view of both hands. Marked bone destruction with replacement by large tophaceous deposits producing deformity is quite evident. Despite the large bulbous deposits, little subluxation has occurred.



FIG 341 (Left) Gout Colored male 37 years old. The patient was severely afflicted with chronic tophaceous gout which is quite rare in this race. Head lateral view. Note the typical tophi of the auricle.



FIG 342 (Right) Gout. (Same patient as Fig 341) Upper extremities. Showing the gross deformities produced by advanced tophaceous gout.



FIG. 343 Gout. (Same patient as Fig 341) Lower extremities. Demonstrating very severe changes in the knees the ankles and the feet with ulceration of the tophus over the dorsum of the left foot.

(Benemid®) salicylates ACTH and cortisone

Isotope studies with radioactive nitrogen 15 administered intravenously or tagged uric acid show that there is what may be termed a "turnover rate" of new uric acid to replace the old. In normal man the amount is 50 to 75 per cent per day of the total miscible pool of uric acid. Normally

the turnover rate is greater than the amount that is excreted in the urine as uric acid.

Furthermore after it is injected as uric acid nitrogen has been found in the urine in the form of urea and ammonia. This clearly demonstrates that normal man can break down uric acid into simpler nitrogenous components. Such a function is described as uricolysis. The mammalian group

excretes the end products of dietary metabolism as urea and is referred to as ureotelic. The reptiles and the birds excrete the end products of dietary metabolism as uric acid and are referred to as uricotelic (see diagram on p. 48)

In some instances there is no doubt about the fact that the miscible pool of uric acid is increased from dietary nitrogen. This occurs in the normal and to a much greater degree in the gouty individual. This was demonstrated by the oral administration of N^{15} glycine. The steps in the degradation of glycine to uric acid are via purine catabolism (see p. 48)

Finally there is the problem of excretion of uric acid itself which undoubtedly is varied in certain individuals. So we may sum up the situation with regard to gout and the elevated uric acid as follows in



FIG. 344 Gout (Same patient as Fig. 341) Anteroposterior views of both elbows. These show marked destruction involving the left lower humerus. There are less marked bony changes in the right. The soft tissue swelling and the tophaceous deposit are considerably greater on the right side.

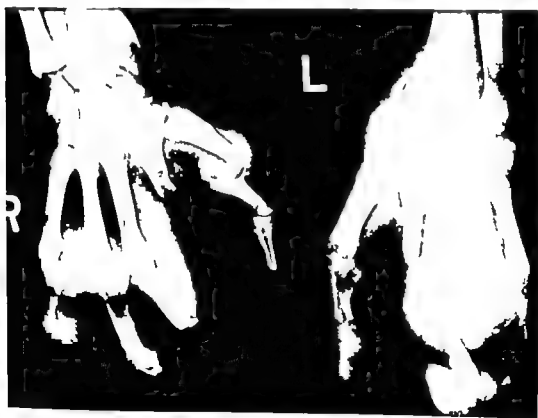


FIG. 345 Gout (Same patient as Fig. 341) Anteroposterior views of both hands. Widespread changes are present. The distal end of the left radius is eroded and irregular. Marked destruction has occurred bilaterally in the metacarpals and the phalanges. Both index fingers have become amputated by the destructive process. There has been partial loss of the right middle and the left ring fingers.

some individuals there is an inability to handle dietary nitrogen intake so that the uric acid will pile up while in other individuals there is an inability to break down uric acid into simpler products such as urea

and ammonia. In a third group there is difficulty with the actual excretion of uric acid

As can be observed the etiology of gout is still unknown.

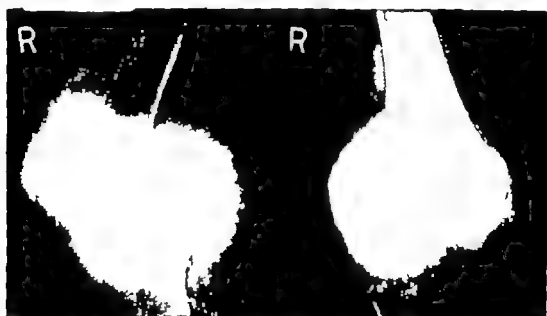


FIG. 346 Gout. (Same patient as Fig. 341) Anteroposterior and lateral views of right knee. There are destructive changes with marked osteoporosis. Note the large soft tissue masses which represent tophaceous deposits. Some calcification is present in these tophaceous collections



FIG. 347 Gout. (Same patient as Fig. 341) Anteroposterior and lateral views of left knee. There are moderate destructive changes and severe osteoporosis. Note the swelling due to tophaceous deposits in the suprapatellar pouch. Considerable degenerative change involving the head of the fibula as a result of invading tophaceous material can be noted.



FIG. 348. Gout. (Same patient as Fig. 341.) Lateral views of both ankles. Advanced destructive changes are evident in the ankle on the left side with practically complete destruction of both the lower tibia and the fibula and the talus. On the right side this destruction is not nearly so advanced but much osteoporosis is evident.

Clinical Features. Gout may be considered to be of two broad types.

1. The acute articular type which eventually may become polyarticular or even involve other elements of the mesothellum.
2. The chronic tophaceous type in which the disease has been present long enough for a large amount of tophi to be deposited and for it to become widespread. Furthermore such chronic cases feed upon themselves in that there are considerable tophaceous deposits to add to the miscible pool of uric acid. This means that more and more these cases become subject to attacks of the disease.

It must be borne in mind that no single

case of gout will duplicate completely or need duplicate completely any other case but the following are salient factors observed in this disease: sudden onset of acute tendinitis, bursitis or arthritis with periods of remission in which complete disappearance of signs and symptoms previously seen occurs. There is a predilection for joints especially those of the feet and most especially of the big toe which is involved in 70 per cent of the initial attacks of gout and eventually may be the site of as much as 90 per cent of the attacks (Figs. 336 to 338). However almost any joint in the body may be involved. The knee is commonly involved but the disease is extremely rare in

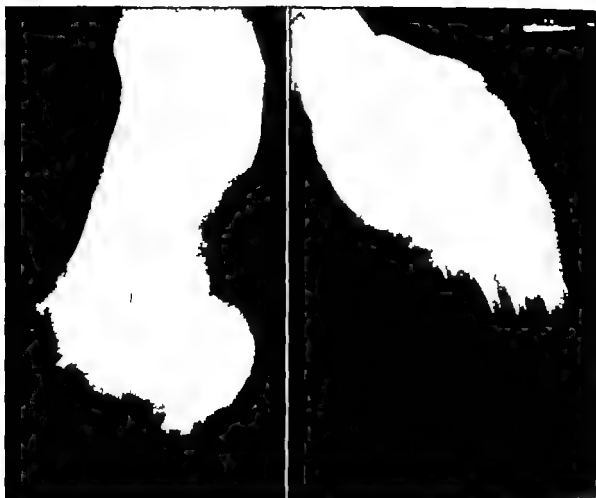


FIG. 349 Gout. (Same patient as Fig. 341.) Anteroposterior views of both feet. The loss of digits as well as the great destruction of widespread nature throughout the feet is quite evident.

the spinal column and in such joints as the sacro-iliac, the temporomandibular and the sternoclavicular.

Gout is predominantly a disease of the male past the third decade of life. Although it is usually monarticular in onset, it may become polyarticular.

In well-developed and long standing cases of gout in particular the presence of tophaceous deposits almost anywhere in the body is to be observed (Figs. 342-343). This occurs however particularly in the ears on the helix or on the antihelix (Fig. 341). Tophi may be observed anywhere else, such as in the tendons of the fingers or the toes over the olecranon over the malleoli or over the knuckles they have even been re-

ported in the aorta the heart valves, the epiglottis and the corpora cavernosa of the penis.

Tophi are painless except when they are the site of an acute attack. They also may become so large and produce so much reaction in the tissue above them that the skin over them may break down. Clear-cut prominent tophi rarely are seen until late in the disease unless the case is very severe. Although, when they do break down these tophi are supposed rarely to become infected since the uric acid is felt to be protective against such an eventuality the authors have observed that severe lymphangitis and lymphadenitis may occur in such cases.

Very important are the factors that precipitate acute gouty onsets or exacerbations of the disease—namely stress phenomena, alcoholism, anesthesia, operations, and excess stresses and strains of a physical nature.

Gout is very rare in Negroes, but again the authors have observed severe disease of a gouty type in Negroes (Figs. 341 to 349).

A systemic effect of gout can be kidney colic with showers of uric acid crystals. Advanced cases may show kidneys and ureters filled with large amounts of tophaceous material. The vascular system may be involved. Deposits may occur in the brain; changes in the eye (such as uveitis) may occur.

Attacks may vary in frequency. Some individuals may have them many times during the year; others may get them only in the spring or the fall; some people may go a year or longer without attacks. The average length of attacks usually ranges about 2 weeks—sometimes more. Even when they are very acute, attacks can be controlled fairly well within this time by adequate medication.

X-RAY FINDINGS. The original x-ray pictures at the onset of the disease are negative (Fig. 335). However, as the process continues—especially the tophaceous phase—actual destructive changes of bone will be observed (Fig. 336). It is not uncommon to find punched-out areas in the heads of the first metatarsal, for instance, which frequently are pathognomonic of the disease (Figs. 337-338). In the late stages, large areas of bone may be dissolved completely and replaced with tophaceous material (Figs. 339-340 and Figs. 344-346, 347 and 348). One can observe practically complete dissolution of an entire shaft of a metatarsal or even the entire portion of a phalanx as well as an entire olecranon (Figs. 345 and 349).

CHEMICAL FINDINGS. The primary chemical findings are an elevated serum uric acid which may be associated with a reduction in uric-acid output and with kidney disease. However, usually kidney disease is not present and uric acid output may be relatively

normal in amount yet a constant build-up of the miscible pool of uric acid continues.

The level of blood uric acid is not necessarily pathognomonic of the acuteness of the disease, for only mildly elevated uric acid levels can be associated with very acute gout, and extremely high uric acid levels observed in the quiescent state. Furthermore, uric acid elevated to quite high levels may be found in members of families who do not show acute gout in its peripheral manifestations at least.

The sedimentation rate may be elevated during the acute attack. Fever and leukocytosis may be observed.

Pathology. There is no specific pathologic finding in acute gout except a nonspecific inflammatory reaction of the areas involved.

The primary consideration is the presence of uric acids in the body fluids; the presence of urates in the tophi and the replacement of normal tissues by infiltration of these tophaceous deposits. Reaction of an inflammatory type occurs secondary to the irritative effect of tophi.

Where bone will show destruction of trabeculae by tophi, the joint surfaces will show considerable pannus formation and even destruction of articular cartilage (Figs. 337 to 340 and 344 to 349). Later, secondary contractures and fibrosis may occur about affected joints.

Tophaceous collections may become ulcerated but these areas usually have a peculiar resistance to secondary infection (Fig. 343).

Differential Diagnosis. Gout must be differentiated from rheumatic fever, rheumatoid arthritis, pyogenic arthritis, syphilitic gumma, and traumatic arthritis as well as gonorrheal arthritis. It also must be differentiated from osteoarthritis, although frequently it is observed to occur concomitantly with it.

Treatment. Treatment of gout may be represented as an approach in at least 3 ways:

1. The pain and the toxicity of the acute attack is handled through the use of colchicine in doses of 1/100 to 1/120 gr. or 0.5

mg repeated every half hour for 6 or 7 doses or until purging or nausea whichever occurs first. Then the patient will feel better as far as the joint manifestations are concerned. At this time administration of colchicine is reduced to 1/120 gr. or 0.5 mg. 3 or 4 times a day.

2. The constitutional treatment is carried out in a dual drive. This would involve reduction of nitrogenous products in the intake and a stimulation to increase excretion of uric acid through the use of uricosuric drugs such as probenecid (Benemid®), phenylbutazone (Butazolidin®), salicylates, ACTH, and cortisone. The dose of probenecid is from 1/2 to 1 Gm. twice daily, occasionally 3 times daily. The smaller dose is considered in the very acute phase because this produces dissolution of tophi and eventually even very large tophi will dissolve. This soluble tophaceous material may add to and increase the miscible pool of uric acid and if this level becomes high enough, acute gouty manifestations may occur. However, if uricosuric drugs are continued indefinitely, one can see how the miscible pool will become lowered even to normal levels. The usual dose of phenylbutazone is 100 mg., 3 times daily. Careful check of blood and platelets must be made, for in some individuals this drug will produce profound effect upon the blood.

Salicylates when given may be given for weeks at a time in doses of not less than 75 gr. or 5 Gm. per day. Eventually the dose is reduced and then stopped. The authors omit 1 day per week, then 2, then 3, until no more salicylate is taken. Probenecid and salicylates should not be given together since they appear to be antagonists as far as their effects on the body are concerned.*

For constitutional management, control of the diet is necessary—a reduction of foods made up of anything that crawls, flies, swims or walks. Furthermore we must consider that there are certain foods which from a clinical basis appear to be high in purines and to favor gouty-attack tendencies and others which appear to combat the ele-

vated uric acid. Glandular meats particularly sweetbreads, liver, kidneys and brains, fish roe, fats, alcohol, legumes—all appear to aggravate gouty diathesis. In the opposing category may be listed milk, cheese, eggs and carbohydrates. A diet can be worked out in which some latitude is allowed particularly after the acute stage is over through a reasonable balance of milk, cheese and eggs versus those foods which are definitely harmful.

3. Finally there is the problem of local management. Excision of large tophaceous areas, especially if they are threatening to break down the overlying skin, is indicated. Careful excision of this material can be followed by primary closure of the skin and excellent healing. This is a good thing to practice in removing tophaceous material from almost any place because such material will produce continued destruction if allowed to remain in situ unless uricosuric agents are used constantly.

Secondly in the acute phase in which large amounts of fluid either containing or not containing tophaceous material are present in joints such as the knee, these joints ought to be tapped and the fluid removed. Local instillation of hydrocortisone in a knee will be helpful. Splinting of acute joints is desirable until the inflammatory process is reduced.

Physical therapy to loosen up contractions and to tone muscles is indicated.

SUMMARY All of the recent investigations, particularly those with isotopic nitrogen, have been done on a pure research basis. It would be of interest to attempt to fit these measures to various individuals suffering from this disease. It appears definite that colchicine will act almost miraculously to combat acute gout, yet it will not affect uric-acid metabolism. Over a long period of time uricosuric drugs reduce the miscible pool so that a reasonably free state occurs if the pool is kept low by continued medication.

Diet appears to be of help in some cases but not in others. It may be that the selec-

tion of cases when diet is to be effective might be ascertained by radioactive isotope studies. In this instance cases unsuitable for diet therapy could be spared the burden of such a regimen.

Certainly the unfortunate victim of gout

may prefer that his disease be abolished with a single well aimed rifle bullet rather than alleviated by a shotgun blast. For present, no such direct course of therapy is available and careful individualized handling is indicated in most instances.

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Neoplasms

PRIMARY MALIGNANT NEOPLASMS OF BONE

The authors' interest in primary bone tumors lies in the consideration of their known biochemical effects. Certain benign lesions of bone have been considered elsewhere in this book. These are not reflected by any abnormal chemical values. They are probably aberrations in bone development. The authors refer to solitary bone cyst (Figs. 40 to 47), enchondroma, solitary and multiple (Figs. 48 to 51 and 53 to 59) and osteocartilaginous exostosis, solitary and multiple (Figs. 60 to 64 and 66 to 72).

The only blood-serum value affected by a known primary bone tumor is the alkaline phosphatase, which appears to be elevated relatively consistently in the osteoblastic form of osteogenic sarcoma¹⁻⁴ (Figs. 350 to 353).

Some workers have attempted to correlate the alkaline-phosphatase level with the activity of the tumor. This concept was based upon reduction of alkaline phosphatase following excision or ablation^{2, 3} and increase of alkaline phosphatase following recurrence of the tumor or when metastases appear.

The data in relation to alkaline-phosphatase fall following excision or ablation for osteogenic sarcoma appear logical. The relationship of increased alkaline phosphatase levels with osteoblastic metastases also appears reasonable. An occasional exception may occur when metastasis strikes the liver to block hepatic excretion. Then elevation of serum-phosphatase levels also will be expected to occur.

These workers also have reported diminution of alkaline phosphatase values following irradiation of osteogenic sarcoma. Since this modality has little influence on such a

tumor, a more reasonable explanation is that the radiation destroys alkaline-phosphatase production in bone. Thereby the amount of phosphatase released into the blood may be reduced.⁵

It appears that the greater the osteoblastic activity, the greater the production of alkaline phosphatase¹ (Fig. 354).

Alkaline-phosphatase values up to 70 have been observed in osteoblastic osteogenic sarcoma. Even moderate elevations in older people may be significant, but it must be remembered that children normally may show alkaline-phosphatase levels up to 12 Bodansky units (Normal range for infants and children 5 to 12; adults 2 to 4.5).

Osteolytic variations of osteogenic sarcoma will show little or no change in alkaline phosphatase.

The cartilage-forming tumors, the chondrosarcomas, whether primary or derived from an enchondroma or the cartilage cap of an exostosis, show no change in blood serum values (Fig. 65).

Occasionally the reaction of the surrounding bone to a Ewing's tumor may be accompanied by an elevation of serum alkaline phosphatase.⁶

METASTATIC TUMORS OF THE SKELETAL SYSTEM

Definition. Malignant tumors which originate outside the skeleton and spread to it by blood stream, lymph channels or direct invasion are termed metastatic.

A primary skeletal tumor would include those tumors that arise from all types of bone cells and their precursors, from all types of cartilage cells and their precursors, and from the cells of the fibrous investments of the skeletal structures. By such a defini-



FIG 350 Osteogenic sarcoma. (Figs. 350-351 from Dr. M. M. Pomeroy.) Adolescent subject. Classic osteoblastic lesion characterized by condensation in the distal femoral metaphysis. It does not appear to cross the epiphyseal line. At the flare of the shaft an area of decreased density suggesting bone destruction is observed. The medial aspect of the lower shaft shows considerable periosteal lifting with new bone formation. This suggests invasion of the subperiosteal area by tumor cells extending through the haversian canals.



FIG 351 Osteogenic sarcoma. (Same patient as Fig. 350.) Amputation specimen. Note the intact epiphyseal plate but the wide expansion of the lesion in the distal metaphysis and the subperiosteal regions. This type of lesion often shows elevation of the serum alkaline phosphatase.

tion a condition such as multiple myeloma would be considered as a secondary neoplasm of bone.

Most workers however widen this classification to include synovial vascular and marrow neoplasms associated with bone and cartilage as primary skeletal tumors. The authors of this book believe that such a thought is a good one since this latter group may present with primary skeletal



FIG. 352 Osteogenic sarcoma (Figs. 352-353 from Dr. M. M. Pomeroy). Sclerosing osteogenic sarcoma of the Dium. This is the type of bone-forming lesion which may be reflected in the rise of the serum and local alkaline phosphatase.



FIG. 353 Osteogenic sarcoma. (Same patient as Fig. 352.) The chest plate shows cannon-ball metastases to lungs.

manifestations and is easier to discuss in this light.

Essentially then a metastatic skeletal tumor is usually an epithelial tumor a carcinoma which has spread to the bones. A primary bone tumor such as an osteogenic sarcoma may present hematogenous skeletal deposits but this is usually only of academic importance. Moreover the multicentric marrow malignancies—myeloma, lymphoma and leukemia—are considered as primary neoplasms and discussed in Chapter 19 (See Table 8, p. 469).

Incidence. Secondary skeletal malignant lesions are decidedly more frequent than primary malignant bone tumors. Of these secondary malignancies of the osseous system the most common are carcinoma metas-

tases by the lymphatics or the blood stream. Occasionally there may be direct extensions of a neighboring soft-tissue malignant tumor into bone.

There is a variable incidence of skeletal metastases depending upon the type of neoplasm. However autopsy studies have shown that there appears to be no type of carcinoma incapable of metastasizing to bone. Coley has used the term *ossophile* to describe carcinomas which have a tendency to metastasize to bone. These include particularly carcinomas of the breast, the prostate, the thyroid and the kidney (Figs. 355-356). It has also been shown recently that many so-called Ewing tumors or endothe- liomas of bone are really metastatic small cell carcinomas of the lungs, the so-called "oat cell" type¹ (Figs. 357-358). However a true Ewing tumor of bone which is highly malignant is also encountered.

Clinical Findings. Osseous pain or even a pathologic fracture may be the first clinical evidence of a neoplasm. Secondary deposits may be noted at any time. This may be

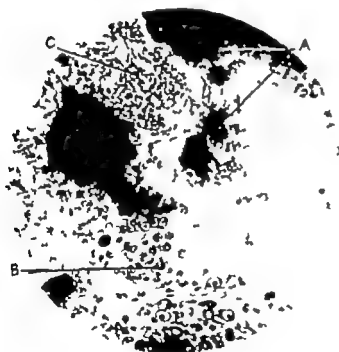


FIG. 354 (Top) Osteosarcoma with newly formed bone lamellae. ($\times 35$) (Bottom) Osteochondrosarcoma with calcified osteoid tissue (A) atypical cartilage cells (B) undifferentiated sarcoma tissue (C) ($\times 80$) (From Ehrlich, W. E. Pathology for Students and Practitioners of Dentistry p. 344 Philadelphia, Lea & Febiger 1941)

prior to the discovery of the primary tumor at the first discovery of the primary tumor or even many years after it has been removed

Atypical bone pain in any individual which is persistent or increasing should alert the clinician to the possibility of metastatic

bone cancer Blood chemical studies, including serum calcium phosphorus alkaline and in the male acid phosphatase, total protein with albumin-globulin ratio complete blood count and sedimentation rate are indicated Urinary studies for calcium excretion and the determination of



FIG 355 Metastatic kidney carcinoma. White female 59 years old. The patient complained of pain in the left arm and the right hip area for 8 months before admission. She tripped and fell at home sustaining pathologic fracture of the upper third of the shaft of the right femur. Biopsy at the time of the open reduction and Küntscher nailing indicated renal origin of the metastatic tumor.

Anteroposterior and lateral views of right femur (*Left*) June 11 1951. A complete fracture with displacement has occurred through an osteolytic area of metastasis at the junction of the upper and the middle thirds of the femur (*Center*) June 18 1951. The alignment is excellent 5 days following open reduction and Küntscher nail fixation (*Right*) July 9 1951. Organizing callus can be seen. Good position is maintained with ambulation.

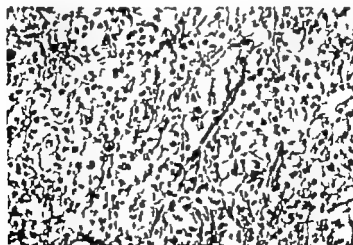


FIG 356 Metastatic renal-celled carcinoma. (Biopsy of case shown in Fig 355) Hematoxylin-eosin, ($\times 120$)



FIG. 357 Metastatic carcinoma of the bronchus. Male 48 years old Intractable pain in the neck was the patient's initial symptom. He was a heavy smoker Biopsy of the cervical spine lesion was compatible with bronchogenic carcinoma. Demise occurred in association with rapid osseous and pulmonary dissemination of the tumor. Oblique view of cervical spine Destruction of the spinous process of the second cervical vertebra by an osteolytic lesion is present.

Bence Jones protein can be done if indicated.

Appropriate roentgenograms should be taken with special views if necessary. Serial studies may be indicated if symptoms and signs persist after a negative first examination.

A history of a primary lesion in the recent or the distant past should be sought (Figs 359 to 361).

Careful physical examination and other clinical and laboratory studies should be made in search of the primary lesion. This is particularly true if there is a possibility of definitive rather than palliative treatment as for example a solitary metastasis



FIG. 358 Metastatic carcinoma of the bronchus (Same patient as Fig. 357). Open mouth view of cervical spine. Destruction of a large portion of the second cervical vertebra has occurred. Note arrows.

from a renal carcinoma or so-called hypernephroma.

In addition hormonal therapy of skeletal metastases makes the determination of the primary lesion of some importance. This may be done by finding the primary growth and/or by pathologic examination of the secondary deposit.

CHEMICAL FINDINGS The blood chemical changes associated with carcinoma metastatic to the skeletal system result from either the destruction or the repair or both, of the involved osseous tissue. Osteoblastic lesions are accompanied by a local and often a general serum alkaline-phosphatase elevation. Purely osteolytic lesions produce little or no rise in the alkaline phosphatase.

The greater the degree of bone destruction the higher may be the serum calcium and phosphorus levels. Probably this eleva-



FIG 359 Metastatic breast carcinoma. White female 64 years old. Admitted one day after a fall with resultant pathologic fracture of the left femur. Past history indicates that the patient had had a radical mastectomy in 1944. Metastatic lesions had been identified in the spine, the lungs and the ribs before the fracture occurred. Anteroposterior and lateral views of left femur (Nov. 1 1951). A complete short oblique fracture is seen through a metastatic lesion at the junction of the middle and the upper thirds of the femur.



FIG 360 Metastatic breast carcinoma. (Same patient as Fig. 359.) Anteroposterior and lateral views of left femur (Feb. 1 1952). These roentgenograms 3 months after Kuntscher nail fixation show excellent alignment and advanced organized callus formation.

tion results from inability of the kidney to excrete the end products of bone lysis rapidly enough. Furthermore, this calcium may be protein bound and therefore not so easily excreted. A serum-calcium content of 13 mg per 100 cc of blood serum or above may cause serious clinical symptoms—nausea, lassitude and even mental confusion. However, this calcium rise is more apt to be of ionizable calcium resulting from rapid release of calcium from the bone or a disuse factor rather than from calcium released by tissue destruction in a protein (globulin) bound form.

Marked osteoblastic lesions may result in severe osteoid hunger for calcium and

phosphorus so that the blood levels and the excretion of these elements will not vary appreciably from the normal. Yet, the alkaline-phosphatase content may become considerably elevated. In these lesions evidences of hypercalcemic toxicity are therefore not seen. It is actually possible for the bone at traction for calcium to be so marked as to cause tetany.

Lesions of a degree intermediate between those which are purely osteolytic and those which are purely osteoblastic may present intermediate blood chemical pictures. In this instance small elevations in alkaline phosphatase, calcium and phosphorus will be observed.

The rise in serum acid phosphatase is now recognized as a most important sign of metastatic cancer of the prostate.

Total protein and albumin-globulin determinations will reveal elevation of the total protein and A/G ratio reversed as a result of euglobulin increase in multiple myeloma. Sternal or iliac marrow examination and the finding of plasma cells in the peripheral blood may be useful in differentiating this condition.

ROENTGENOGRAPHIC DIAGNOSIS. It has been shown many times that a normal roentgenogram does not exclude small metastatic foci in the marrow spaces. This is true particularly of the spine. The earliest evidence of a small metastatic lesion is an alteration of the trabecular pattern. Progressive irregularity and destruction of the lamellar bone occur. Finally confluent irregular areas indicate progressive invasion.

Spontaneous fracture of a long bone is in-

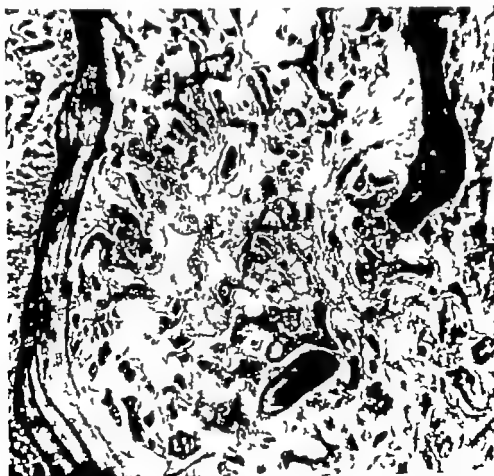


FIG. 361 Metastatic breast carcinoma. (Same patient as Fig. 359.) Hematoxylin-eosin. ($\times 60$)



FIG 362 Metastatic breast carcinoma (From Dr Eugene I Pendergrass) White female 41 years old Improvement of osteolytic skull metastases with testosterone therapy Lateral views of skull (Left) August 25 1952 Advanced multiple osteolytic lesions are present in the calvaria. (Right) September 15 1953 Healing has occurred with filling in of many of the lesions in the skull vault.

dicative of a pathologic fracture. A smooth rounded margin with evidence of bone destruction on the roentgenogram is commonly found in metastatic lesions (Figs. 355 and 359). Sudden or persistent pain in the back with or without radiation in girdle fashion makes the spine suspicious.

In cases of vertebral collapse differentiation between myeloma and osteolytic carcinomatosis is often difficult. Fortunately the differentiation is reasonably certain in that multiple myeloma will show at least one of the following signs: Bence Jones proteinuria, plasma cells in peripheral blood or sternal-puncture fluid, and elevation of the total serum-protein level with reverse of the albumin-globulin ratio.

Localization of osteolytic metastases is usually in the medullary cavity. If progressive destruction occurs, areas of tumor tissue coalesce to give a punched-out appearance.

Sometimes so-called military carcinomatosis is present. Here destruction is principally microscopic and the roentgenogram will produce only a washed-out appearance that is indistinguishable from osteoporosis, osteitis fibrosa of hyperparathyroidism, or

multiple myeloma. Areas of destruction should be sought even if the magnifying glass is needed.

Cortical implantation is also seen. Expansion of the cortex, however, is rare and usually indicates a slow-growing lesion. It is not infrequent in the solitary metastases of a kidney carcinoma.

Osteoblastic metastases are usually from the prostate but occasionally mammary lesions will stimulate a bone-formative response. The new bone induced by the tumor obliterates the trabecular pattern of the involved area. The pattern is usually diffuse but cannon ball solitary osteoblastic reactions do occur.

Pathology. Metastasis by retrograde lymphatic extension favors bone nearest the primary growth. Thus mammary carcinoma favors the ribs, the thoracic portion of the spine and the skull. In prostatic cancer it is the sacrum, the lumbar portion of the spine and the pelvis which most commonly are involved (Figs. 363 to 365). Hematogenous metastatic deposits may occur in any of the bones, however, they are seen only rarely distal to the knees or the elbows.



FIG 363 Metastatic carcinoma of the prostate. White male, 59 years old. Rapidly progressing pain in the right hip and the left leg was the earliest symptom in this case and alkaline phosphatase determination was significantly elevated.

Anteroposterior view of pelvis. An osteoblastic bone reaction is seen in the iliac bones and extends on the right body of the ischium on the left to include the rami of the ischium. There are also changes of osteoblastic nature in both femora. A condensation is observed in the sacral regions bilaterally. It must be remembered that this location is a frequent early site for this metastatic lesion.



FIG 364 Metastatic carcinoma of the prostate (Same patient as Fig 363). Complete relief of bone pain but no resolution of roentgenographic changes followed orchietomy and estrogen administration. Eventually these lost their effect and further temporary relief was obtained with roentgen therapy. Cordotomy was finally required several months before death. Anteroposterior and lateral views of lumbar spine. The third lumbar vertebra is observed to be quite dense, a so-called "ivory vertebra." Not only osteoblastic metastatic changes in both iliac bones adjacent to the sacrum. Condensation of bone is present on the posterosuperior surface of the third lumbar vertebra.

There are two principal forms of bone metastases: osteolytic and osteoblastic. The osteoblastic lesion arises as a bone formative reaction to the stimulus of the tumor depositing in that area (Figs 363 to 365). It

is not a metaplastic manifestation of the tumor itself. A similar bone formative reaction is observed in sensitive osteoblastic lesions following hormone administration or roentgen therapy (Fig 362).

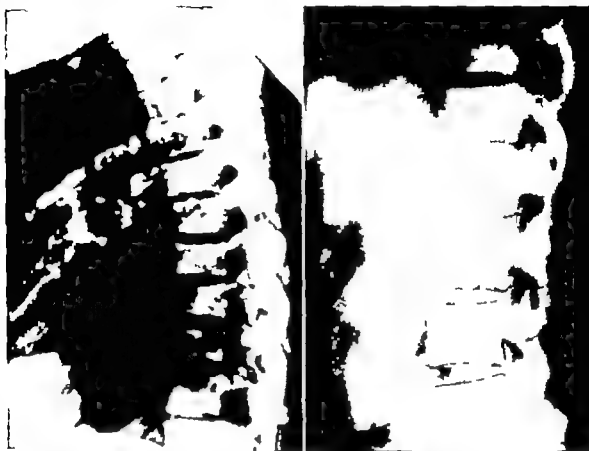


FIG. 365 Metastatic carcinoma of the prostate. White male 61 years old. Advanced carcinomatosis from the prostate. (*Top left*) Lateral view of thoracic spine. Multiple small islands of bone-formative reaction have occurred in response to the neoplasm. The associated osteolytic areas give a honey-combed appearance. (*Top right*) Lateral view of lumbar spine. This shows primarily osteoblastic response throughout the vertebral bodies. (*Bottom*) Anteroposterior view of pelvis and lower lumbar spine. The lesions are primarily osteoblastic. Again, however, zones of osteolytic destruction do exist throughout the pelvis and the upper femora.

Most osteoblastic lesions result from carcinoma of the prostate. Occasionally a breast lesion may present a similar picture.

In an osteolytic lesion the bone tissue in the metastatic mass is destroyed (Figs. 356 and 361). Occasionally the tumor mass may stimulate a peripheral osteoblastic reaction in which instance there will be osteosclerosis or periosteal new bone formation surrounding the lytic lesion.

Biopsy is usually indicated particularly if the primary tumor is unknown (Fig. 356). Moreover a history of malignancy does not always mean that a given lesion is necessarily derived from this particular primary growth.



when rapid downhill course was evident, indicating that little benefit can be attributed to subjective improvement alone. However the comfort of the patient was enhanced regardless.

7 Increase in weight, 71 per cent—an anabolic effect

8 Increase in libido 37 per cent

9 Clitoris enlargement 28 per cent

Miscellaneous effects were drowsiness, nausea, vomiting, edema and hypercalcemia.

Specific side effects of estrogens statistically were alike whether synthetic or natural. However some patients did better on one form, others on another. Side effects from dosages listed above were:

1 Anorexia 57 per cent

2 Nausea, 58 per cent

3 Vomiting 32 per cent

4 Nipple pigmentation 80 per cent

5 Areolar pigmentation 77 per cent

6 Axillary pigmentation 40 per cent

7 Breast engorgement 20 per cent

8 Breast tenderness 16 per cent

9 Vaginal bleeding 33 per cent

10 Withdrawal bleeding 42 per cent

11 Urinary urgency and incontinence 28 per cent

12 Edema, 34 per cent

It is thus obvious that hormones administered in this way proved not to be a panacea for many cases benefited not at all from either hormone. In fact some cases have been aggravated by estrogens, the so-called estrogen-dependent type of mammary cancer.⁴

The important thing therefore is to attempt to separate those cases which may be expected to respond to hormone therapy from those cases which may not be expected to respond. Furthermore it would be helpful to determine if possible, those cases which will respond to androgens and those which will do better upon estrogens.

Pearson et al.⁴ attempted to differentiate those cases of carcinoma of the breast with osseous metastases into two forms called estrogen-dependent and non-estrogen-dependent. Their method consisted of study

ing premenopausal women with carcinoma of the breast metastatic to bone during the menstrual (ovulatory) cycle following surgical removal of the ovaries and then following subsequent administration of estrogens. They indicated that by these methods there are two types of mammary carcinoma, one estrogen-dependent and the other non-estrogen-dependent.

The estrogen-dependent form shows increased calcium excretion during the menstrual cycle and with the onset of menstruation. At the conclusion of the menstrual cycle there is a prompt fall in urinary calcium-excretion levels although not to normal figures. Following surgical castration calcium excretion decreases to normal levels. If estrogen is administered after castration urinary calcium-excretion levels rise.

The non-estrogen-dependent variety shows no fluctuation during the progression of the menstrual cycle or the onset of menstruation. Surgical castration results in no alteration in urinary calcium-excretion figures. When estrogen is given following oophorectomy a reduction in the loss of calcium through the urine occurs but not to normal levels. When the estrogen is stopped urinary calcium excretion again rises with concomitant hypercalcemia.

Certain therapeutic measures have been postulated by these workers on the basis of this evidence. The response of the estrogen-dependent metastatic type appears to be good following castration. These measures may be supplemented by the use of testosterone or its nonmasculinizing counterpart, Stanoalone. Adrenalectomy may be indicated to remove secondary sources of estrogenic hormones. In addition hypophysectomy may be considered further in order to suppress all adrenal function including that of any possible accessory adrenal tissue.

In the non-estrogen-dependent group on the contrary estrogenic hormone would be indicated. Oophorectomy would be of no value. The consequent other measures to get rid of estrogenic hormones secreted by the adrenals would also not be indicated. It is

of particular interest that these workers report the presence of an occasional non-estrogen-dependent type of metastatic carcinoma even in premenopausal subjects.

An as yet unexplained phenomenon in this series was observed in that certain non-estrogen-dependent cases, adrenalectomy gave temporary benefit. This should not have been expected on theoretical grounds since the removal of further endogenous estrogenic hormone could not have been expected to help these cases. Furthermore when symptoms recurred following adrenalectomy, cortisone administration gave a further remission. Here again the postulated value of cortisone was on the basis of suppression of residual adrenal accessory tissue.

It would therefore appear that further studies with a careful evaluation of the effect of cortisone on both the estrogen as well as the non-estrogen-dependent type of cases is indicated in the future.

Carcinoma of the Prostate. Carcinoma of the prostate is of great interest because of the widespread osteoblastic metastases which are common in this condition (Figs. 363 to 365). Also it is of interest because the acid and the alkaline phosphatase of blood serum are elevated. Furthermore it is often quite difficult to differentiate the roentgen picture from that of Paget's disease of bone (Figs. 288, 294).

There is no intention of detailing the enormous amount of research by urologists in regard to benign hyperplasia or malignancy of the prostate. Some points, however, must be touched upon once more in passing.

MacCallum¹ suggested that there are two gonadotropic hormones produced by the pituitary. The first has specific effect upon the testicular germinal epithelium. This is called the follicle-stimulating hormone (FSH).² The second gonadotropin presumably affects the interstitial cells of Leydig. The testosterone thereby secreted by these cells affects the prostate and the seminal vesicles. This is referred to as the interstitial-cell-stimulating hormone (ICSH).² It

is also possible that this gonadotropin may stimulate that part of the adrenal that is active in producing androgens.

Endocrine influences in carcinoma of the prostate have been proved by temporary control of the disease by castration.³

The antithesis of this thought that androgen will stir quiescent malignant foci in the prostate into activity is suggested. As a result, the use of even small doses of testosterone in men beyond the age of 50 has been condemned.⁴ This particular thought is not substantiated fully. It is true that when some cases of prostatic carcinoma have been controlled with estrogen in small doses (25 to 50 mg.) the beneficial effect has been neutralized by the simultaneous daily dose of 10 mg. of testosterone propionate. But this is the case in malignancy that is not a quiescent focus. Furthermore many cases of carcinoma of the prostate develop when no testosterone has been administered. Finally carcinoma of the prostate occurs usually after age 60 although it may appear at considerably earlier ages. When it does usually appear the androgen-producing tissues are theoretically in their waning period so less active androgen function is expected.

Balance studies in large numbers would help further to clarify the relationship of prostatic cancer and androgen-excretion levels. For example at present we cannot differentiate androgens of adrenal origin in the urine from androgens of testicular origin. Furthermore like carcinoma in other areas it is known what may at times aggravate it when it is developed but it is not known what may initiate it. This means the carcinoma either develops or quiescent foci become activated when excess androgen is not the rule. There is some as yet unknown relationship between the Leydig cells and the seminiferous tubules.

It is of interest that studies on a patient with a malignancy of the interstitial cells showed a 17 ketosteroid excretion of 1.015 mg. per 24 hours yet there was no prostatic carcinoma here. Of course one can argue that this case had no quiescent foci.⁵

The pattern of 17 ketosteroid secretions in patients with carcinoma of the prostate as compared with normals⁶ showed that etiocholanolone ranged up to 120 to 200 per cent of the amount of androsterone in cases of benign hypertrophy or carcinoma of the prostate. In normals this value was approximately equal—in fact there is usually more androsterone than etiocholanolone.

Latent carcinoma has been described as averaging 14.8 to 16.6 per cent. These small cancers are similar to clinical prostatic carcinoma on anatomic and histopathologic bases. Early carcinoma originated from the peripheral prostatic tubules in 87.5 per cent of cases. Frequently it was discovered in the prostate in more than one focus.⁷

Much argument has been advanced with out convincing proof that there is a direct relationship between prostatic hypertrophy and prostatic carcinoma.

It appears that there may be an indirect correlation between nodular hyperplasia and prostatic carcinoma, however. This is based on a tie in that both are associated with disturbance of hormone balance as a common incitor.

Diagnosis. Any male past 50 who has symptoms of prostatic enlargement should be examined carefully. If he has had back ache, double care with careful radiographs on repeated occasions is indicated.

Frequently the diagnosis is made by histologic examination in a case which has previously been considered to be one of benign prostatic hypertrophy. The carcinoma may arise from any part of the anterior, the lateral or the posterior lobes.

Frequency of involvement of the posterior and the peripheral portions of the gland facilitates extension along the perineal lymphatics to metastasize to the pelvis and thence to the lower spine in particular.

Treatment. When prostatic carcinoma is found early, radical excision of the prostate with the seminal vesicles and the bladder neck is indicated.⁸ Furthermore in 100 radical prostatectomies a 5-year cure rate was 51.7 per cent. However in 42 patients followed up to 12 years, 26 of them were alive and apparently well without such treatment.⁹

Hormonal therapy is advised by urologists only if excision of the gland cannot be done or if there has been a recurrence.

Metastatic bone lesions may or may not cause pain. If bone pain is minimal, castration or enough estrogen to produce mild feminization is advocated.¹⁰ If symptoms of metastasis are severe, both castration and large estrogen doses are considered (Figs. 363 to 365). 0.1 mg. of estinyl is a small dose for mild cases. 10 or more times this dose may be used when symptoms are severe.

Some increase in 3- and 5-year cures has been reported following endocrine therapy.¹¹

Among interesting possibilities for further effective therapy is bilateral adrenalectomy with sustaining doses of cortisone. This is to rid the patient of adrenal androgens by adrenalectomy as well as testicular androgens by orchiectomy.

Use of enormous doses of cortisone will also reduce adrenal function, but side effects are such that the surgical approach may be more reasonable.

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SICKLE CELL ANEMIA

(Syn Mönchocytosis drepanocytic anemia.)

Definition. This is a severe hemolytic anemia with characteristic sickle-shaped red blood cells and is both hereditary and familial. It has been reported to occur almost exclusively in persons with partial or complete Negro ancestry. It was first described by Herrick in 1910.²

Incidence. It is probable that between 5 and 10 per cent of all American Negroes show sickling traits. However, only 1 out of 40 who show sickling traits have true sickle cell anemia.⁴ The disease is a Mendelian dominant.

Clinical Characteristics. These include (1) chronic anemia and jaundice, (2) aching pains, particularly in the extremities, and



FIG. 366 Mediterranean anemia (From Dr. Eugene P. Pendergrass) White male 23 years old. Lateral view of skull. Marked osteoporosis, thinning of the tables and widening of the diploë are present. Perpendicular striated trabeculae are particularly prominent in the vertex.

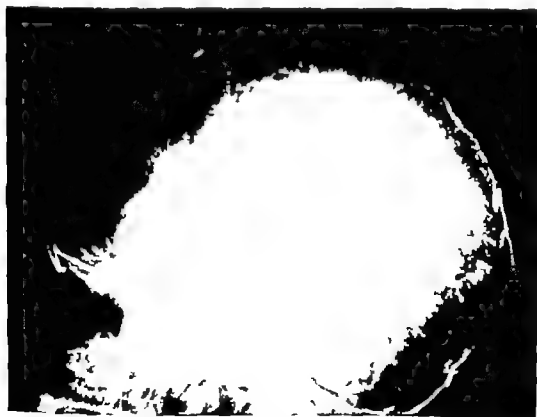


FIG. 367 Mediterranean anemia. (Figs. 367 to 373 from Dr. Eugene P. Pendergrass) White male 12 years old. Lateral view of skull. Osteoporosis of the calvaria is evident with perpendicular striations of the occipital area. The diploë is increased in width and the tables are thinned.



FIG 368 Mediterranean anemia. (Same patient as Fig 367.) Right and left shoulder girdles with portions of rib cage. Anteroposterior views. This demonstrates the classical widening of the medullary cavity with coarse weblike bone trabecular structure. This component is so prominent as to appear cyst like. The cortices are thinned. Changes are more apparent about the humeri and the scapulae but may be noted in the ribs also.

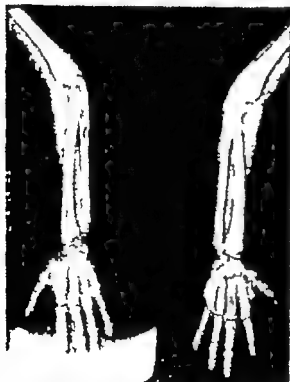


FIG 369 Mediterranean anemia. (Same patient as Fig 367.) Anteroposterior views of both forearms and hands. Prints are reversed. The bones of the metacarpals and the phalanges are rectangular in shape. This results from expansion of the shafts. In addition all the bones show widening of the medullary cavities, osteoporosis, thinned cortices, and prominent coarse trabeculations.

the joints (3) acute abdominal crisis simulating an acute surgical abdomen (4) leg ulcers especially about the malleoli (5) epistaxis (6) multiple central nervous system symptoms and (7) bone and joint changes.³

Marrow overgrowth is less marked than in Mediterranean anemia. Adults may have bone pains associated with the roentgenographic appearance of new bone formation on the endosteal surface of the cortices of long bones.

LABORATORY FINDINGS. Blood findings are a severe anemia with counts as low as 1 to 2 million red blood cells per cubic millimeter. Stain smears in some cases may reveal changed red blood cells of sickle-cell shape. Other cases require special anoxic sickling

preparations to demonstrate these abnormal cells.

Nucleated red cells and target cells also are seen. Leukocytosis with a shift to the left is a frequent finding and may be confusing in instances of abdominal crisis.

The resistance of red cells to hemolysis by hypotonic saline is increased.

CHEMICAL FINDINGS. These include elevated serum bilirubin and increased urobilinogen. Despite the anemia, the sedimentation rate is not increased due to the fact that sickle cells resist clumping.

FIG. 370 (Right) Mediterranean anemia. (Same patient as Fig. 367.) Lateral view of lumbar spine and pelvis. The bone structure shows thinned cortical elements and widened cancellous spaces with coarse and prominent trabeculae.

FIG. 371 (Bottom) Mediterranean anemia. (Same patient as Fig. 367.) Anteroposterior view of pelvis. There are generalized osteoporosis, thinning of the cortices and prominent coarse weblike trabeculations.



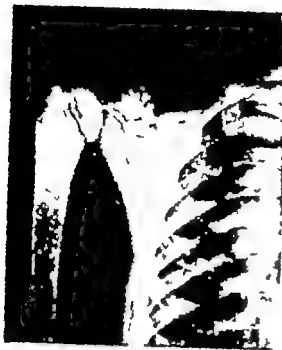


FIG. 368 Mediterranean anemia. (Same patient as Fig. 367) Right and left shoulder girdles with portions of rib cage. Anteroposterior views. This demonstrates the classical widening of the medullary cavity with coarse weblike bone trabecular structure. This component is so prominent as to appear cyst like. The cortices are thinned. Changes are more apparent about the humeri and the scapulae but may be noted in the ribs also.

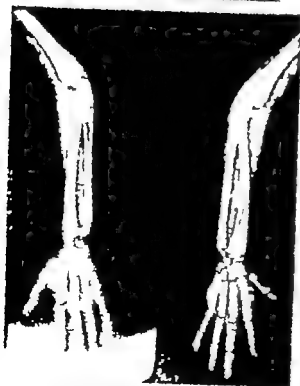


FIG. 369 Mediterranean anemia. (Same patient as Fig. 367) Anteroposterior views of both forearms and hands. Prints are reversed. The bones of the metacarpals and the phalanges are rectangular in shape. This results from expansion of the shafts. In addition all the bones show widening of the medullary cavities, osteoporosis, thinned cortices and prominent coarse trabeculations.

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X RAY FINDINGS Bone changes are not uncommon.² These are similar to the changes in Mediterranean anemia (Fig 374). A peculiar finding is the development of endosteal cortical new bone formation in contrast with medullary widening in adults. Bone changes in children are very rare.^{2,3}

FIG 372 Mediterranean anemia. (Same patient as Fig 367.) Anteroposterior views of both femora. The coarse trabecular pattern is especially prominent at the lower thirds of the femora. There is a tendency to flaring at this area. The cortices are thinned, and generalized osteoporosis is present.

FIG 373 Mediterranean anemia. (Same patient as Fig 367.) Anteroposterior views of both feet. The rectangular shape of the phalanges and the metatarsals is to be noted. There are, in addition the characteristic osteoporosis, thinned cortices and weblike coarse trabeculations.





FIG. 345 Skull anemia (11-year-old M. M. Lencarz). Anteroposterior and occipital views of skull. The cancellous type of bone increased in thickness and especially in the occipital view of the parietal bone trabeculae radiating perpendicularly from the plane of the inner table. The interorbital table is very thin in the frontal area.

In addition there are changes seen which based on aseptic necrosis and probably due to thrombotic infarction of bone. Femoral head in particular appears like those found in Legg-Perthes disease (Fig. 346).

Pathology. The bone marrow was markedly hyperplastic even to invasion of the normal fatty marrow spaces. Large numbers of nucleated red cells are found. In addition the white cells in the marrow were shifted to the left.

Hemosiderosis (iron pigment deposit) are formed throughout the reticulo-endothelial system.

Multiple thrombotic areas occur throughout the viscera and are followed by necrosis and hemorrhage.

The changes in the central nervous system are predominantly on a multiple thrombotic basis.

CONGENITAL HEMOLYTIC JAUNDICE

(See Congenital hemolytic icterus, chronic familial jaundice, hemolytic neonatorrhea, chronic acholuric jaundice, chronic spherocytic anemia, globe-cell anemia, hydrops fetalis.)

Definition. This is a hemolytic anemia re-



FIG. 375 Sickle-cell anemia. Colored female 19-year-old Loma, standing history of multiple swollen tender joints, immitation, rheumatic fever. Present complaints are related to the left hip area. Sickling tests on the red blood cells were repeatedly positive. Anteroposterior view of pelvis. Moderately increased trabeculations are evident in the pelvis. Aseptic necrosis is present in the head of the left femur. At open operation the articular cartilage of the femoral head was found to be wrinkled. The underlying ulchondral bone was necrotic.

sulting in jaundice and splenomegaly. It is congenital and always familial.

Incidence. It is the most common of all familial hemolytic anemias and appears to be a Mendelian dominant which may be transmitted by either side. It is very rare in Negroes. Acquired hemolytic anemias are much more common. Sickle-cell anemia is also more frequent.

Clinical Characteristics. Manifestations occur at various times from birth to later life. Recurrent bouts of jaundice and anemia may be the findings in milder cases. At times the onset may be abrupt with a crisis at other times it may be gradual.

Severe cases show intractable jaundice of a nonpruritic type with anemia. There is a high incidence of cholelithiasis and biliary tract disease due to bilirubin stones, a common finding.

The spleen is enlarged markedly in nearly all cases. Often hepatomegaly may also be found. Leg ulcers occur but to a less common degree than in sickle-cell anemia. Physical stigmata often observed include tower skull (high vaulted skull), polydactylia, brachydactylia and dental and palatal defects.

LABORATORY FINDINGS. The anemia may be variable. It may be severe during crises with the red blood count to as low as 1 million. When the disease is quiescent no anemia may be evident. The characteristic cell is a round bright spherical (not biconcave) cell. Such a cell since it is not biconcave will have no central pallor. This cell is called a spherocyte showing a characteristic diagnostic increased hemolysis in hypotonic saline. Reticulocytosis is a constant finding in the peripheral blood.

Leukocytes are normal or are only slightly increased except in acute crisis when severe leukocytosis with a shift to the left may be found.

CHEMICAL DATA. Chemistry studies demonstrate elevated serum bilirubin and increased urobilinogen in urine and stool.

X-RAY FINDINGS. Bone changes are similar to those observed in sickle-cell anemia

and Mediterranean anemia, but to less marked degree. Particularly evident are striations in the frontal and the parietal areas of the skull.

Pathology. The spleen is enlarged and is filled with closely packed red blood cells. The liver and other reticuloendothelial organs show increased iron pigment. Bilirubin stones occur frequently in the gallbladder. Red-cell hyperplasia of the normoblastic type is seen in the bone marrow.

Treatment. Splenectomy is almost uniformly beneficial. This is followed by remission of the jaundice and a rise of the red cell count. Spherocytes however may persist with increased fragility. Appropriate biliary-tract surgery may be indicated.

Prognosis. The untreated disease is related to the time of onset. The earlier the disease begins the poorer the prognosis. However splenectomy improves the outlook whatever the age of onset. Latent (low grade) cases may require no treatment.

SKELETAL MANIFESTATIONS OF LEUKEMIA

Definition. Leukemia is a malignant process involving the white-blood-cell elements of the bone marrow. The proliferation of these leukemic cells results in the replacement of the hematopoietic marrow spread into the fatty marrow and dissemination into the various tissues and organs of the body. Generally speaking the abnormal immature white blood cells appear in the peripheral blood. If the white blood count remains normal, the disease is termed aleukemic.

Clinical Features. Leukemias are differentiated for purposes of classification on the basis of the type of white cell which is primarily proliferating. Myelogenous or myeloid leukemia is manifested by proliferation of one or more of the granular series of leukocytes. The lymphocyte or one of its precursors is involved in lymphogenous or lymphatic leukemia. Some workers recognize a monocytic type of leukemia.

Further differentiation is on the basis of the time factor or rapidity with which the disease runs its fatal course. The acute variety most frequently affects children or young adults. Here the typical is commonly a lymphatic leukemia, although mixed varieties do exist.

In older individuals, the leukemia is commonly a chronic one. The cell implicated are generally of the myeloid series. Chronic lymphatic leukemia does, however, occur.

Chronic myeloid leukemia with a terminal acute or chronic acceleration in intensity may also be a clinical feature of osteosclerotic anemia, advanced Mielz-Schönberg disease or marfan's disease.

The earliest clinical manifestations of acute leukemia usually are based upon a concomitant overgrowth of the white blood cell involved and depletion of the red blood cells and the platelets. Anemia, weakness, fever and hemorrhagic phenomena are noted very early. In the common form of acute leukemia seen in children, which is lymphatic in variety, there is also an associated depression of the granulocyte series. This agranulocytosis is manifested very frequently by overwhelming infection involving particularly the oral cavity and the upper respiratory tract. Sometimes the entire body defense mechanism fails and complete and overwhelming sepsis occurs.

In acute leukemia, skeletal manifestations in some cases may be the earliest manifestation. These include rheumatic like pains of the bones and the joints which may simulate rheumatic fever or even osteomyelitis. These skeletal symptoms and findings usually are seen in children and are less common in adults.

In the usual case of acute leukemia, the classical findings mentioned above do occur and the clinician is able to make the diagnosis by this picture and confirm it on a hematologic basis. Occasionally, however, the presenting musculo-skeletal pain remains a predominant feature for a long time. They may lead the attending physician astray and cause him to overlook the necessary



Fig. 3-6 Acute leukemia (From Dr Edward B. D. Neuhauser) White male, age 24, died 8-19-49 of acute myelogenous leukemia. Anteroposterior view of upper extremities. Marked destructive changes are present in all the bones. Periosteal lifting and reaction have occurred secondary to the invasion by the neoplastic tissue.

blood and marrow studies for diagnosis.

Chronic leukemias, both myelogenous and lymphatic, have in general no skeletal manifestations of importance. They are chronic in course and insidious in onset. They affect primarily the bone marrow, the lymph nodes and the various reticulo-endothelial organs such as the spleen and the liver. They are included in this discussion principally because occasionally they may present a characteristic radiologic picture in the bones.

These radiographic findings usually are only of incidental importance but in isolated cases they may be of diagnostic significance.

RADIOGRAPHIC FINDINGS. It has been noted that lymphatic leukemia is asso-

sulting in jaundice and splenomegaly. It is congenital and always familial.

Incidence. It is the most common of all familial hemolytic anemias and appears to be a Mendelian dominant which may be transmitted by either side. It is very rare in Negroes. Acquired hemolytic anemias are much more common. Sick-cell anemia is also more frequent.

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In older individuals the leukemia is commonly a chronic one. The cells implicated are generally of the myeloid series. Chronic lymphatic leukemias do however occur.

Chronic myeloid leukemia with a terminal acute or subacute acceleration in intensity may also be a clinical feature of osteosclerotic anemia, advanced Albers-Schönberg disease or "marble bones."

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FIG. 376. Acute leukemia. (From Dr. Edward B. D. Neuhauser.) White male born 9-27-47, died 8-19-49 of acute myelogenous leukemia. Anteroposterior views of upper extremities. Marked destructive changes are present in all the bones. Periosteal lifting and reaction have occurred secondary to the invasion by the neoplastic tissue.

blood and marrow studies for diagnosis.

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These radiographic findings usually are only of incidental importance but in isolated cases they may be of diagnostic significance.

ROENTGENOGRAPHIC FINDINGS. It has been noted that lymphatic leukemia is asso-



FIG. 377 Acute leukemia. (From Dr Edward B D Neuhauser) White female admitted at the age of 3 weeks 10-13-46 died 11-17-46 of acute myelogenous leukemia. At the age of 3 weeks, an abscess was noted at the umbilicus when the cord separated. (Left) Anteroposterior view of lower extremities (Oct. 15 1946) Meta physal rarefaction is striking in both upper and lower femora and tibiae (Right) Anteroposterior view of lower extremities (Nov 8 1946) The medullary destructive process has progressed rapidly in 3 weeks. In addition early periosteal proliferation is evident.

ciated more commonly with osseous changes than the myelogenous variety. About 7 per cent of a series of cases with leukemia showed bone changes in the x ray picture.¹

Radiographic findings have been noted as follows:

1 Generalized osteoporosis sometimes very slight

2 More specific areas of rarefaction. These may be isolated or may become confluent (Figs 376-377). In the long bones these rarefied areas may be longitudinal in direction.¹

3 Subperiosteal formation of new bone is seen (Figs. 376-377). In general this subperiosteal new bone is laid down in a longitudinal or onion peel fashion rather than in a perpendicular or sunburst manner in relation to the shafts of the long bones.

4 Pathologic fractures have been noted and are frequently through an area of previous osteolysis. There may be evidence of some callus formation.

5 The skull shows involvement of the diploë and the inner and the outer tables by

zones of rarefaction. In addition there may be subperiosteal new bone formation in the calvaria.

Röntgenographic changes in the skeleton in children afflicted with leukemia are similar to those found in adults.² Diffuse osteoporosis, specific areas of radiolucency and subperiosteal new-bone proliferation.

One characteristic finding in children present only because of the open epiphyseal plates, is the early appearance of a transverse radiolucent zone at the juxta-epiphyseal region of the metaphysis of the various long bones³ (Fig 377). This finding is not specific for leukemia; in milder degree it can be noted in any severe systemic disease of the growing child. In these instances it appears to represent a diminution of bone formation at the epiphyseal plate. In scurvy the scurvy line or "Gerustmark" is a similar phenomenon representing an area of deficient fibrous-tissue ingrowth as a result of the vitamin-C deficiency.

In leukemia, this radiolucent zone in the metaphysis appears to represent the destruction of the newly laid down bone trabeculae at the epiphyseal plate as a result of the invasion of the leukemic tissue.

It has been noted that these rarefied zones will disappear during remissions, whether spontaneous or following treatment by radiotherapy or chemotherapy.

LABORATORY FINDINGS. Diagnostic laboratory findings in leukemia are established on the basis of white blood counts, peripheral blood smears and bone-marrow examinations. The latter are done on the basis of aspirations or biopsies.

In chronic myelogenous leukemia the white blood count is generally elevated and ranges between 100,000 to 800,000 white blood cells per cu mm. Peripheral blood smears show an enormous pleomorphism of the granulocyte series.

In chronic lymphatic leukemia the white blood count may not reach the extremely high levels of the myeloid variety. It generally ranges between 200,000 to 300,000 white blood cells per cu mm. The peripheral

blood smears show large numbers of relatively uniform looking white blood cells of the lymphocyte series.

There is sometimes a concomitant depression of the red blood cells and the platelets.

In acute leukemia special stains may be necessary of both the peripheral blood smear and the bone marrow studies in order to distinguish an acute myeloid from an acute lymphatic leukemia. By demonstrating the presence or the absence of granules in the "blast" cells one can differentiate whether they belong to the granulocyte or the lymphocyte series. In addition monocytic varieties have been noted. Actually the differentiation is largely of academic importance since all varieties of acute leukemia rapidly terminate fatally.

Particularly confusing from the diagnostic point of view may be those cases of the so-called aleukemic variety. This term refers to those cases in which the total leukocyte count is normal or subnormal. It does not infer that there are no abnormal immature cells present in the peripheral blood. In these cases single or certainly repeated examinations of peripheral blood smears or of the "buffy coat" will show the presence of immature abnormal white blood cells even in an aleukemic case.

Bone-marrow studies are not necessary for a definitive diagnosis in all cases of leukemia. However they are mandatory in the aleukemic variety where the peripheral blood smear gives only presumptive evidence. Moreover aleukemic episodes have been noted occasionally in otherwise classic cases of both myelogenous and lymphatic leukemias of the acute and chronic types. It has been suggested that as many as 10 per cent of all cases of leukemia are aleukemic.⁴

It is these aleukemic cases in children which may be difficult to diagnose early. The peripheral blood counts are normal and the occasional abnormal white blood cell may be overlooked on a white blood smear. There are only vague musculoskeletal symptoms. However the presence of osseous x-ray findings noted above should lead to

definitive bone marrow studies. These alone will make the diagnosis of leukemia and save the patient unnecessary or improper treatment.

Pathology In chronic myelogenous leukemia, the principal changes lie in the bone marrow and in the spleen. Both the normal red marrow and the fatty marrow are replaced by leukemic tissue. The neoplastic tissue fills the marrow cavity and enters the subperiosteal regions via the haversian systems. The haversian canals are widened and eroded by the leukemic cellular proliferation.

The medullary bone trabeculae are thin, the cortical bone is eroded and the periosteum is lifted. New bone formation may occur in a subperiosteal fashion.

As a result of the involvement of bone pathologic fractures may occur. There may be evidence of callus proliferation in an attempt at healing. With intramedullary fixation of long bone pathologic fractures actual bone healing may occur if the course of the disease permits.

In the myeloid variety liver, kidneys, lungs, lymph nodes and skin may be invaded by the proliferating myelogenous leukemia tissue.

In the chronic lymphatic variety the earliest neoplastic proliferation of the white blood cells begins in the lymph nodes. Eventually bone marrow, spleen and bones may become involved.

Treatment. Treatment of acute leukemia is generally unavailing. It is a matter of days, weeks or at the most months the course of the acute forms of leukemia is generally not over 100 days. Folic acid antagonists as well as cortisone, ACTH and purine derivatives are the present agencies of choice in acute leukemia of children.³

Therapeutic agents for the chronic varieties of leukemia are legion; they will not be discussed here. It is definite however that none of them has been curative. It is also well to insert the note of caution that since many cases of leukemia show spontaneous remissions, the remission

following the use of a given agent may be attributable to the disease itself rather than to the new drug being used.

Therapeutic agents may be divided into the following groupings.⁴ The first are the so-called *supportive measures* used. These include blood transfusions which must eventually be used in almost all cases of chronic leukemia. Analgesics and sedatives are also indicated as needed.

Inhibitory drugs are those which inhibit cell growth by interfering with intracellular enzyme systems. These include the oil of Fowler's solution employing arsenic. Colchicine is a similar older agent. X-ray therapy is a most successful and well-established device coming under this heading. More recently radioactive phosphorus, nitrogen mustard, urethane and triethylene melamine have been used.

There are also the so-called *competitive agents*. These drugs compete with the leukemic cell for metabolites. They include the antifolic acid derivatives and 6-mercaptopurine.

General *stimulating drugs* such as ACTH and cortisone also have been tried but they have been only temporarily effective.

Prognosis. Leukemia of all types is fatal sooner or later. The acute variety is generally fatal in less than 3 months. The remission may come even more rapidly than this.

The chronic cases may do rather well for a number of years even before therapy is started. They may remain clinically all though not hematologically in a state of remission.

In some instances there is a terminal acute exacerbation before death ensues in the chronic cases. At this point the chronic case will usually become refractory to any form of treatment.

SKELETAL MANIFESTATIONS OF MALIGNANT LYMPHOMA

Definition. By malignant lymphoma is meant a cancerous condition beginning in the lymph nodes or other lymphatic tissues.

In order of decreasing incidence the generic group includes Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma and giant follicle lymphoma.

For the purposes of our discussion we are concerned with these lesions as they affect bone. Commonly this is by direct extension or by vascular or lymphatic metastasis. In some rare instances certain of these entities may be considered to have arisen as primary tumors within a bone itself.

Incidence. These lesions affect males in greater proportion than females, averaging about two to one. Hodgkin's disease is generally found in the age group between 20 and 40. The other lesions affect an older group ranging between the fourth and the sixth decades in highest incidence.

Clinical Features. The site of origin for most malignant lymphomas is the cervical lymph nodes. However other lymphatic changes not infrequently may be the primary site of departure for these entities before they disseminate.

In discussing osseous manifestations of these lesions it is important to realize that there is a difference in incidence between clinically ascertained dissemination of malignant lymphomas and the incidence of autopsy findings of osseous spread of the tumor. Obviously those cases affected with osseous symptoms during life or cases in which osseous lesions are determined on the basis of clinical findings such as biopsy or roentgenographic study will be considerably less in incidence than those cases subjected to full autopsy. The millary seeding of the marrow cavity may not be detected during life but will raise the incidence of positive osseous dissemination at autopsy to much higher figures.¹

It is not the purpose of the authors of this book to discuss the cases in which the primary findings are not related to the skeletal system. Sometimes in the course of the systemic dissemination of the malignant lymphoma there may be spread to one or more parts of the skeleton but these bony

deposits are of small moment in the generalized process.

The authors are concerned with emphasizing that skeletal lesions occasionally may be the initial or at least the early manifestations of these entities. The important initial complaint is that of pain. This is frequently evident in the vertebral column especially the thoracolumbar areas. This pain may be of a dull aching type or rather severe and sharp in nature. Sometimes there is girdle radiation as the result of pressure on nerve roots associated with osseous destruction in the vertebral column. Sometimes the pains may be intermittent in nature at first and simulate rheumatism or fibrositis. The mildest analgesics may appear to help and work up is mistakenly deferred.

The flat bones such as the ilium may harbor the presenting lesions. A scapula or a rib may also be the focal site calling attention to the patient's condition.

As with other malignant metastatic lesions in long bones a pathologic fracture occasionally may call attention to the entity.

From the point of view of incidence it has been estimated that 10 to 20 per cent of Hodgkin's disease will present clinical skeletal involvement¹ this is confirmed by other workers.^{2,3}

Lymphosarcoma has a lesser but similar clinical picture in relation to the skeletal system. Craver and Copeland³ found bone metastases in 17 (10.4 per cent) out of 164 cases of lymphosarcoma by biopsy or autopsy. In lymphosarcoma it is also important to remember that terminal dissemination of the lesion as a lymphatic leukemia may occur in which case the lesion is very widespread and comes under the category of lymphatic leukemia (discussed above).

Giant follicle lymphoma rarely affects bone in its early relatively benign stage. As the disease progresses the lesion converts generally into a lymphosarcoma and it inherits the characteristics of this lesion.

While reticulum-cell sarcoma may also disseminate and involve the skeleton it has

also been considered that there is a primary reticulum-cell sarcoma of bone.⁴ When it is primary this lesion appears to show a preference for the long bones such as the femur the tibia and the humerus. However it may begin in the axial skeleton or even in the skull or the hands and the feet. Here again symptoms are those of pain and disability related to the part affected.

LABORATORY FINDINGS: There are no diagnostic findings in malignant lymphoma. Certain findings, however, are suggestive, particularly when evaluated in light of the clinical and the radiographic picture. This is especially true in relation to Hodgkin's disease. Particularly important from the point of view of corroborative data has been the examination of the respective components of the peripheral complete blood count.⁵

The anemia found in these entities is a reflection of the degree of invasion and destruction of the bone marrow. In general in early cases there may be little or no anemia found but with later progression it is frequently seen.

The greatest degree of anemia is found in Hodgkin's disease. Lymphosarcoma less frequently shows more than mild depression of the red blood count.

In all malignant lymphomas the total leukocyte count may be normal, elevated or depressed. Leukocytosis, however, is seen more commonly in Hodgkin's disease than in the others. On the contrary leukopenia is more frequent in the other forms than in Hodgkin's disease.

In Hodgkin's disease the differential count again is not diagnostic but certain common findings not infrequently are seen. These include neutrophilia, relative and absolute lymphocytopenia, monocytosis and eosinophilia. Various combinations of any or all of these may be noted in various cases. In Hodgkin's disease the fall of the neutrophil count to subnormal levels is usually an indication of rather widespread dissemination. On the other hand it has been emphasized that an absolute increase of

lymphocytes is very rare in Hodgkin's disease as opposed to lymphosarcoma.⁶

In lymphosarcoma and even in giant follicle lymphoma, a relative or absolute increase of the lymphocyte count is not uncommon. Moreover in lymphosarcoma particularly leukemoid blood pictures not infrequently are seen. While the leukemic cells are commonly small lymphocytes, occasionally immature lymphoblasts or monocytes are noted in significant numbers.

It must not be forgotten that lymphosarcoma in its terminal stages or even in intermediate stages, not infrequently may be indistinguishable hematologically from a chronic or even an acute lymphatic leukemia.⁷

The platelet counts are generally normal until marrow invasion is such as to result in a thrombocytopenia. During this invasion stage bizarre irritative forms of platelets may be seen in the peripheral blood. Occasionally in Hodgkin's disease the platelet count may be elevated.

Bone marrow studies have been done in many of these cases but here again the findings are not diagnostic. However in lymphosarcoma where there are abnormal cells found in the peripheral blood, it is mandatory to make a bone marrow study to rule out a full blown leukemic picture.

In Hodgkin's disease the bone marrow may reveal a slight shift to the left in the myeloid elements, monocytosis or eosinophilia. This is in keeping with the peripheral blood picture noted above.⁸

If the area aspirated or biopsied has been involved by Hodgkin's disease tissue it may be possible to ascertain the presence of the diagnostic Reed-Sternberg cells. In this case bone marrow biopsy rather than aspiration puncture would be more useful as it would afford a larger amount of tissue for examination.

Lymphocytes may be relatively increased in the bone marrow of a lymphosarcoma even before a full leukemic picture has supervened.

Blood chemical changes may be of im-



FIG. 378 Malignant lymphoma. Hodgkin's disease. White male 15 years old. Anteroposterior and lateral views of lumbar spine. Destructive spondylitis of the first and the second lumbar vertebrae with laminographic study. Note the preservation of the intervertebral disk space despite considerable destruction of the vertebral bodies. This is important in differentiating this from tuberculous spondylitis in which the disk space is usually involved. Diagnosis was made by examination of a supraclavicular lymph node (From J. Internat. Coll. Surgeons 20:183, 1953)

portance in the accumulation of further presumptive evidence for the diagnosis of malignant lymphomas particularly when they involve the skeletal system. None of these findings is diagnostic.

Calcium and phosphorus levels in the serum are generally normal. Occasionally if bone destruction is great enough hypercalcemia and hypercalciuria may be noted.⁹ In association with this hypercalcemia and hypercalciuria balance studies occasionally have revealed negative calcium balance.¹⁰ In cases associated with bone formative reaction so-called osteoblastic type of metastases elevated alkaline phosphatase may be present.¹¹

Other findings include an almost constantly elevated blood sedimentation rate and an occasionally elevated blood uric acid.⁹

Galloway¹² noted the presence of Bence Jones protein in the urine of a patient with Hodgkin's disease. This finding has been

confirmed by other workers in isolated instances of this particular form of malignant lymphoma and also in disseminated lymphosarcoma, with skeletal involvement.

Certain other workers¹³ have reported the presence of relatively elevated globulin levels above the highest normal values in 23 per cent of Hodgkin's cases. These usually were associated with significant decreases in albumin levels so that the total protein level itself usually was not altered. However, fractionation into the albumin and the globulin components would reveal significant changes in such instances. By comparison a similar finding was found in 33 per cent of cases of myelogenous leukemia.

X-RAY FINDINGS Most workers indicate there is no diagnostic roentgenographic picture in this group of disease entities when they involve the skeletal system.

Uehlinger¹⁴ collected from the literature 83 cases of Hodgkin's disease showing



FIG 379 Malignant lymphoma. Hodgkin's disease. (Same patient as Fig. 378.) Chest plate. The first film shows some widening of the mediastinum. This is due to lymphadenopathy. The second film shows considerable increase of the process. The third film shows partial regression after nitrogen-mustard therapy. Ofttimes, severe bone destruction will occur in this condition before much change will be observed in the chest or other soft tissues. (From J. Internat. Coll. Surgeons 20:184, 1953.)



FIG 380 Malignant lymphoma. Hodgkin's disease. (From Dr. M. M. Pomeroy.) Anteroposterior view of shoulder. Note destructive process in the humerus. These lesions are osteolytic and multiple. Note the tendency to confluence. There is also cortical invasion on the medial side with periosteal reaction. Some cases may show some osteoblastic reaction. This is not so here.

skeletal x-ray changes and noted the following proportion of involvement: vertebrae 62.6 per cent, pelvis 21.8 per cent, sternum 15.7 per cent, ribs 10.8 per cent, scapulae 2.4 per cent, and clavicles 2.4 per cent.

Bone lesions may be primarily osteolytic or in some instances osteoblastic. In Hodgkin's disease the lesions are generally mixed in type.¹⁸

In lymphosarcoma, on the other hand, the lesions are predominantly osteolytic in about 85 per cent of cases.¹⁸

The osteolytic lesions of Hodgkin's disease and lymphosarcoma reveal single or multiple areas of trabecular destruction. These areas may vary in size from almost indiscernible pinpoint zones to larger confluent areas of radiolucency (Figs. 378 and 380). Cortical invasion is not uncommon and destruction of the cortex with periosteal lifting frequently is noted.

In the vertebral column the finding resembles that of metastatic carcinoma. The intervertebral disk space generally is well preserved, a finding of important differentiation from tuberculosis of the spine (Fig. 378). Involvement of the lymphatic chain overlying the vertebral column may result in paravertebral shadows simulating those seen in tuberculous spondylitis but the

preservation of the intervertebral disk space ■ a distinguishing factor

In Hodgkin's disease, not infrequently there ■ a mixed reaction with osteoblastic zones being found along with the osteolytic areas, both in the vertebral column the skull the pelvis and the long bones

In some cases of Hodgkin's disease and very rarely in lymphosarcoma ■ pure osteoblastic reaction is noted This may be so pronounced in a vertebra as to result in the roentgenographic diagnosis of ivory vertebra

Occasionally a distinguishing finding in these lymphoid skeletal lesions is the presence of cortical implantations as opposed to the purely medullary deposits of multiple myeloma.

In primary reticulum-cell sarcoma of bone there is a rather strong tendency for the bone lesion to break out into the soft parts, with widespread local infiltration as well as the bone destructive findings in the x-ray picture. This lesion is principally osteolytic in type but with destruction and invasion of the cortex, periosteal new bone formation may be stimulated.

Pathology Pathologic findings are primarily those of the respective lesions themselves.

Grossly one may find more or less wide spread seeding of the bone marrow the cortex and even the subperiosteal areas if the cortex has been invaded and infiltrated. Coalescence of the foci may be noted with the presence of larger areas of bone destruction The neoplastic tissue is generally firm in consistency and yellowish in color Secondary hemorrhage and necrosis may be present. If much osteoblastic reaction has occurred there may be bony hardness as a result of the proliferation of new bone in response to the neoplastic tissue

In most cases with concomitant lymph node involvement in one or more areas these invaded chains may be suitable for biopsy and may assist in making the diagnosis with or without the necessity for examining the bone (Fig 378) In instances

where the primary manifestation is skeletal and the lymph node involvement is deep-seated or not yet present osseous biopsy may be the only diagnostic step to take

The histologic characteristics in each of these entities have been well covered in detail elsewhere.¹

In summary we may say that Hodgkin's disease is distinguished by certain histologic peculiarities The diagnostic Reed Sternberg cells are large cells containing either a single rather enormous nucleus or multiple nuclei It is felt that these probably are derived from the cells of the reticulo-endothelial network of the lymph nodes or the bone marrow A pleomorphic cellular reaction frequently is noted including eosinophils lymphocytes, neutrophils, plasma cells and fibroblastic reaction. Focal necrosis is not uncommon Later on, a secondary reactive scarring with proliferation of fibroblastic tissue and collagen material sets in This may make certain areas difficult to study

In lymphosarcoma, the proliferating cell is characteristically ■ small lymphocyte Occasionally lymphoblasts of a more immature type are the predominating cellular pattern

Histologic criteria for reticulum-cell sarcoma are somewhat complex Certain cases present findings which on microscopic examination make it difficult to distinguish them from Ewing's sarcoma or even metastatic carcinoma In general the characteristic cell seems to resemble a monocyte It presents a fairly large nucleus which occasionally may have cytoplasmic processes. The nucleus may be eccentric, and even if without processes may be indented In certain other instances the cell is even larger and represents the lymphoblasts seen at the germinal centers of lymph nodes

Treatment. Treatment may be divided into general and local Under general treatment are the supportive measures such as blood transfusions which may be given to relieve the secondary anemic state of the patient.

Radiotherapy is the palliative treatment of choice. Inhibitory agents such as nitrogen mustard, urethan and triethylene melamine have all been used occasionally with temporary success. Stimulative agents such as ACTH and cortisone have played some role here but they appear to be less effective even on a temporary basis than in leukemia.

Pathologic fractures require treatment if the patient's general condition permits. In the long bones intramedullary fixation has been the authors' method of choice.¹⁶

The authors similarly have had experience with a rare case of Hodgkin's disease manifesting primarily in the thoracic spine where it simulated a tuberculous spondylitis. Successful palliation by spinal fusion relieved symptoms, giving complete comfort until terminal dissemination of the Hodgkin's disease occurred some time later.¹⁹

Primary reticulum-cell sarcoma when localized in one bone is generally best approached by amputation or ablation. This is necessary because the local lesion tends to spread rather widely and is very painful in its destructive local advancement. Such instances should be followed by local radiotherapy.^{2, 17}

Prognosis. The prognosis is fatal in all of these entities. Some patients go on rapidly to a fatal denouement. In others the course is more protracted, lasting up to 5 or even 10 years. The clinician must be especially guarded in his approach to the problem as the histologic findings are often not indicative of the ultimate rapidity with which the disease will progress to its end. As long as the general condition of the patient remains favorable one must be on the surface optimistic. The end stage usually comes rapidly with quick progression and imminent termination.

MULTIPLE MYELOMA

(Syn: Kahler's disease, myelomatosis)

This most interesting and complicated disease has been a subject of many thorough and detailed published studies. The

purpose of the authors is to present the typical form of this disease when the bone is involved and to attempt to correlate certain consistent chemical findings with the clinical and the radiologic picture (See Table 8 p 469).

Historical Notes. Bence Jones¹ reported finding in the urine the protein that bears his name. This is a protein which precipitates on heating and redissolves at the boiling point. McIntyre² studied the patient whose urine Bence Jones had examined. He found softening and fragility of the bones.

In 1873, von Rustitzky³ described multiple destructive marrow tumors. These originated in the medullary cavity and eroded the cortex.

Kahler⁴ wrote the first composite of this picture in which bone changes plus the Bence Jones proteinuria were correlated. It has often been referred to since this time particularly in European literature as Kahler's disease.

Since this time there has been a voluminous literature on this subject. Continued work has unearthed many interesting facts about this disease. Hypercalcuria and negative calcium balance were described more than 30 years ago. Hypercalcemia was noted in 1927⁵ and hyperproteinemia was described in 1899.⁶

Incidence. The disease is reported by some to be more than twice as frequent in males as in females^{4, 6} but others disagree. It is rarely found below age 30 and its diagnosis in a child must be questioned seriously. Then it may well be a leukemia or Ewing's tumor or neuroblastoma or a lipoid granuloma. The most common age period for its occurrence is between 40 and 60.

Etiology. The cause of multiple myeloma is unknown. Myeloma cells formerly were divided into four classes: (1) plasma cells, (2) myeloid cells, (3) erythroid cells and (4) lymphoid cells. This listing recently has been abandoned in favor of the concept that it is a single cell observed in different phases.

The present opinion as to the origin of the exact cell is still divided between plasma

of the marrow hemocytoblasts and plasma cells.

Some myelomas show large cells predominating. The theory has been advanced that these that show consistent Bence Jones proteinuria and plasma protein increase 'Bence-Jones' hypothesized that multiple myeloma is a disturbed protein metabolism similar to Niemann-Pick's disease as an interference of lipid metabolism.

Clinical Characteristics. The clinical picture includes the following symptoms: (1) Pain of the vertebral column or the rib cage articular which is often girdlelike, it is neuralgic in character and usually insidious in onset. (2) Loss of weight. (3) Fatigue, general lassitude (often resulting from anemia). (4) Pathologic fracture and (5) Enormous mass if the lesion is superficial, usually over a flat bone as the skull, the ribs or the clavicle.

The disease process may vary from very mild, indolent form to severe cachexia with a swollen shell of a patient. The disease progresses slowly or very rapidly. At times it may start as a simple lesion in a vertebral body, for instance. It may continue dormant for years and then suddenly terminate with an early fatal termination.

Primary Involvement. This includes polyarthritis, emphysema, pleurisy, and terminal pneumonia.

Patients often show thoracic deformity, chronic bronchitis with productive cough, mucopurulent exudation is common occurring in 55 per cent of cases.⁷ Such individuals commonly demonstrate emphysema, which change also considered to result from thickening of the alveolar walls following reactive changes.

Pleurisy in fibropurulent type or even empyema has been reported.⁷ Changes including one or even all of the above often result to progressive disease and to terminal pneumonia.

Neurologic. With the widespread involvement of the skeleton and often of extracranial structures by this disease, nerve damage and neurologic symptoms often re-

sult and may be myriad in type. Those more commonly observed are:

1. Radiating rootlike pain, particularly of the thorax, is common. When severe, collapse of the spine occurs, paraplegia often results. The onset of paraplegia may be gradually progressive, starting only as a sense of weakness of the lower extremities. This steadily progresses to complete paraplegia. The onset can also be sudden with complete paralysis following a sudden collapse of an involved spine area.

2. Rarer neurologic complications are diplopia, failing vision and partial or complete paralysis of the upper extremities.

Gastro-intestinal. This includes nausea, vomiting and cramplike pain, either on a hypercalcemic basis or associated with compression and nerve-root pressure.

LABORATORY DATA. Bone-marrow aspiration or biopsy shows typical myeloma cells in 80 per cent of cases. This may precede any visible osseous involvement. Specific abnormal blood chemical findings in this disease are: (1) Hypercalcemia with normal alkaline phosphatase. (2) Hyperproteinemia due to elevation of serum globulin. There is an associated increase in the sedimentation rate. (3) Tendency toward elevation of uric acid, especially when there is kidney damage. (4) Tendency toward elevation of blood phosphorus, particularly when there is kidney damage. (5) Tendency toward elevation of N.P.N.

Specific abnormal urinary findings are: (1) hypercalciuria (increased urine calcium excretion) and (2) Bence Jones proteinuria in approximately 60 per cent of cases.⁷

Hypercalcemia is a frequent finding when skeletal involvement is severe. One half of proved cases of multiple myeloma show it.¹²

When hypercalcemia occurs, often there are also the symptoms of nausea and abdominal pain, which probably are on a hypercalcemic basis. This has been confused with hyperparathyroidism¹² and in this case, as in others, normal parathyroid glands were extirpated.

On pure chemical analysis, this condition

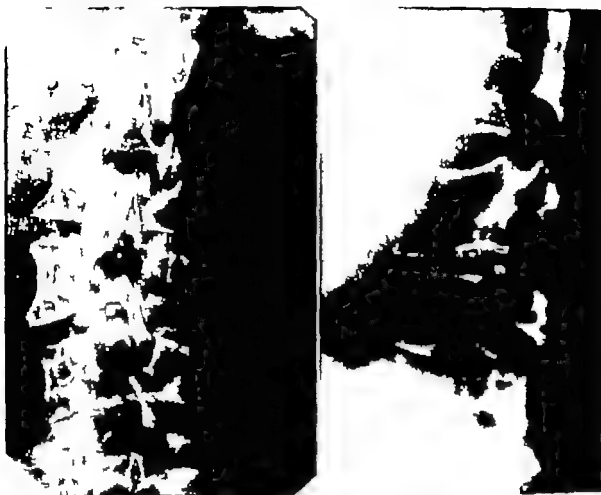


FIG. 381 Multiple myeloma. White male 34 years old. The initial complaint was pain in the midlumbar area. The earliest roentgenograms in 1934 revealed a destructive lesion of the third lumbar body which was thought at that time to be a giant-cell tumor. Initial bone survey was negative. Roentgenotherapy was given with some slight relief of pain but no reconstitution of bony architecture. Back pain recurred within 6 months accompanied by weakness and lassitude associated with severe anemia. Later roentgenograms indicated widespread dissemination of neoplastic tissue throughout the skeleton. Sternal marrow examination was indicative of multiple myeloma. Death occurred soon after this series of roentgenograms were taken.

Spot anteroposterior and lateral views of lumbar spine (1935). The initial destructive lesion of the third lumbar vertebral body is shown. Associated with this, these late films show advanced osteoporosis and washing-out of trabecular detail in all the vertebrae. Only the subchondral end plates of the vertebral bodies show well.

even when associated with hypercalcemia should not be confused with hyperparathyroidism. The blood-serum phosphorus is usually normal unless kidney involvement causes hyperphosphatemia but never will multiple myeloma show hypophosphatemia. In addition balance studies in multiple myeloma do not show a constant negative

calcium balance.¹⁴ Moreover the hypercalcemia which may occur is found only when there is hypercalcemia. Those with normal blood calcium have normal urinary calcium excretion.¹⁵ The hypercalcemia probably is due to skeletal breakdown for it does not represent totally ionizable calcium. In some instances some increased ionizable calcium

may be present. Then symptoms of hypercalcemia may present themselves. Finally, hyperproteinemia will be found frequently in multiple myeloma. Alkaline phosphatase levels are usually normal. In rare instances they may be elevated. These findings are not characteristic of hyperparathyroidism. Alkaline phosphatase and serum calcium are always elevated in that disease.

The hyperproteinemia in multiple myeloma has long been of interest. Attempts have been made to correlate this with the Bence Jones protein. The serum albumin is normal as a rule. When the globulin is markedly increased, the albumin may be decreased.

When the globulin is determined by salting out with sodium sulfate (the Howe method)¹⁶ the elevation of the globulin is of the euglobulin factor.

Sometimes the protein fraction that is increased represents pseudoglobulin I and/or pseudoglobulin II.

From a clinical pathologic point of view an increased globulin can be determined. One method is the formol gel test. In this reaction 2 drops of Formalin are added to 1 cc. of serum. The reaction is positive if the mixture solidifies within 24 hours. This reaction occurs when the globulin exceeds 3.8 mg per 100 cc.¹⁷

The second test is the Sla globulin test. This consists of the addition of 0.02 cc. of blood to 0.6 cc. of neutral distilled water. If the blood is normal, the hemolytic solution remains clear. If there is increased globulin, there is turbidity.¹⁸

When correlated with the Howe method and immunologic technic, electrophoretic studies show 3 groups.¹⁹ In the first group



FIG. 382 Multiple myeloma. (Same patient as Fig. 381.) White male, 34 years old. Lateral view of skull. Multiple small discrete lytic areas are seen throughout the calvaria. These lesions simulate metastatic carcinoma. Diagnosis depends on sternal puncture and blood chemical studies. See text.

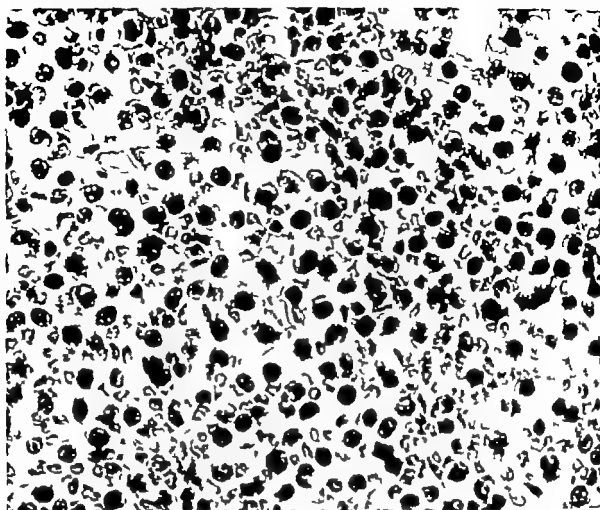


FIG. 383 Multiple myeloma. (Same patient as Fig 381) Myeloma cells, some showing clock nucleus, are seen. Hematoxylin-eosin ($\times 730$)

the euglobulin of the Howe method is found by electrophoresis to be largely gamma globulin. These cases showed very little Bence Jones proteinuria. In the second group where there was normal euglobulin with elevated pseudoglobulin by the Howe method, electrophoresis showed abnormal beta globulin components. These cases had excess Bence Jones proteinuria. The third group had normal serum protein by the Howe and the electrophoretic methods but showed increased Bence Jones proteinuria.

Bence Jones protein in blood and in urine was determined on the basis of the very sensitive immunologic method of Bayne-Jones.²⁰ Bence Jones protein is not a single protein but a collection of proteins.¹⁹

It therefore appears that the protein blood and urinary findings cannot be correlated exactly. The probability is that the globulins come from the tissues. Snapper considers the Bence Jones protein to come from the inclusion bodies in the plasma cells. It appears that elevation of plasma protein with special reference to globulin is a more consistent finding in multiple myeloma than the Bence Jones proteinuria. It is, therefore, a better diagnostic test.

ROENTGENOGRAPHIC DIAGNOSIS The roentgenographic findings must be considered from two points of view: first the distribution and secondly the type of lesion that appears in the bone itself. The changes are predominant in the trunk, the sternum

the ribs the spine and the skull. When long bones are involved the pelvis and the shoulder girdle also show change.

The bone lesions are multiple and represent erosion from the medullary cavity into and through the cortical bone.

The characteristic lesion is an osteolytic one. The size varies from a few millimeters in diameter to 5 or more centimeters in size (Figs 382-384). The tumor produces punched-out rounded areas with little or no condensation surrounding it. Often these areas of destruction coalesce to give an appearance of marked generalized bone de-

mineralization similar to that of osteitis fibrosa generalisata.

The ribs may show superimposed tumors which actually are subpleural ones.

The spine may show little at the start or later may show a single lesion much like a giant-cell tumor (Fig 381). Later marked destruction may be evident (Fig 385).

In the skull there is no increased width of tables. The multiple foci of 'punched out' areas are found in the frontal and the parietal regions (Figs 382-384).

The pelvis shows change ranging from a few cystlike lesions to entire involvement



FIG 384 Multiple myeloma. Colored female 67 years old. Admitted in December 1949 with complaint of increasing inability to walk. The findings were those of spastic paraplegia. A myelogram revealed a block at the ninth thoracic vertebra. Exploratory laminectomy performed in March, 1950 revealed a large extradural tumor. The biopsy report on this mass was plasmacytoma. Sternal marrow puncture also revealed plasma-cell infiltration. Following roentgenotherapy there was some improvement in the power of the patient's lower extremities. This case was published previously in J. Internat. Coll. Surg. 20:181-182, 1953. Lateral view of skull. Multiple discrete osteolytic areas are present.

FIG 385 Multiple myeloma. (Same patient as Fig 384) Anteroposterior and lateral views of lower thoracic spine. Destruction and compression of the ninth thoracic vertebral body can be seen



FIG 386 Multiple myeloma. (Same patient as Fig 384) A pathologic fracture occurred in October 1950 at the upper third of the left femur while the patient was being turned in bed. Anteroposterior and lateral views of left femur. A short oblique fracture is present at the junction of the middle and the upper thirds of the shaft. The marrow cavity shows diffuse infiltration by the myeloma process.

of the structure. In that instance wide spread destruction of bone substance will appear much like osteitis fibrosa generalisata.

Pathologic fractures are common (Figs 386-387). The lower ribs are very prone to fracture when bone destruction progresses far enough.

The spine eventually may show severe dissolution of bone with compression fractures usually multiple. Often they are severe enough to produce compression of the cord and paraplegia (Fig. 385). The intervertebral disks may disappear. Increased kyphosis, lordosis or scoliosis may occur coincident with fracture and collapse of bone.

In the long bones, the usual findings are multiple punched-out areas (Figs 386-387). These vary in size from several millimeters to larger osteolytic zones aggregating several centimeters in diameter. The ribs and sometimes the limb bones may show cystic changes. In rare cases the destructive process is diffuse giving only an osteoporotic appearance without specific zones of radio-opacity.

There is no osteoblastic reaction or periostitis as a rule unless pathologic fracture has supervened. Here callus formation is minimal as shown in the x-ray picture although healing may occur particularly after intramedullary fixation of a pathologic fracture (Fig. 387).

Pathology in Bone: Gross Appearance. There is considerable variation in the degree of involvement of bone by the tumor tissue. Some cases may show no gross change; others for a long time may show only a solitary lesion of the skeleton; still others may show generalized and severe lytic destruction. The lesions are dark red or gray. They are pliable and show hemorrhage, necrosis and pathologic fracture frequently. Tumor may infiltrate diffusely or occur in discrete masses of varying size. Pathologic fractures usually follow invasion of the cortex with perforation into the surrounding soft tissues.



FIG. 387 Multiple myeloma. (Same patient as Fig. 384.) Küntscher nailing was performed on November 6, 1950, after transfusions were given to correct the severe anemia. A Parham band was used as supplementary fixation. The patient was very much more comfortable and could be turned freely in bed. Anteroposterior and lateral views of left femur (February 1951). Excellent callus formation and organization are present. Alignment is satisfactory after Küntscher nail and Parham band fixation.

MICROSCOPIC APPEARANCE. There appear to be two cytologic groups. One is characterized by a small cell similar in some respects to a plasma cell. It is not identical with a plasma cell, however. The second is a larger cell more like a reticulum cell (Fig. 383).

An example of the first group is the round or oval cells which are relatively uniform in size. These cells have a nucleus which fills most of the cytoplasm. They measure approximately 5μ in diameter. The nuclei are dark-staining and stippled with an occasional perinuclear halo. The nucleus is said to demonstrate a spokelike arrangement—so-called cartwheel nucleus. This nucleus is eccentrically placed within a

clear-staining cytoplasm usually eosinophilic.⁸

An example of the second group is a larger cell measuring approximately 10 μ . This cell has a paler variably shaped, stippled nucleus set either centrally, or eccentrically in the cytoplasm. Snapper⁹ considers these to be ribose nucleic acid.

While in a particular case either the large or the small cell may predominate there may be combinations of both. More over some cases may show an intermediate sized cell and others multinucleated cells.

Extraskeletal Pathology Extraskeletal lesions are not common but they have been reported. Autopsy in this case¹⁰ showed only extraskeletal lesions without demonstrable destructive bone lesions. The only lesions which were the extraskeletal ones were characterized by collections of plasma cells in the liver surrounding many of the central canals. Plasma-cell collections were also in different parts of the liver lobules. The lungs showed peribronchial collections of plasma cells, lymphocytes and occasional granulocytes. Mesenteric nodes showed diffuse hyperplasia with infiltration of the pulp with plasma cells.

The majority of cases are primarily skeletal with extraskeletal lesions as concomitant findings which often are of a microscopic nature only.

It can be said that there are reports of infiltration of any or all organs.

A coincident complication of this disease is amyloidosis. This is related to the excess serum globulin and perhaps to the Bence Jones proteinuria.

The interesting variation of amyloid deposition in multiple myeloma is that it is different from the classical secondary form which is amyloid disease following chronic suppurative infection. It is more like the primary type varying in that it is much more diffuse.

It deposits in muscles, bones, joint capsules and throughout the skeletal connective tissue. Skin, subcutaneous tissue and all

other tissues—even the heart—may be involved.

Chemically this amyloid may differ from the usual one. It will not give the typical staining reaction that is diagnostic of the usual amyloid disease.

The kidneys are affected chiefly by involvement with hyaline plugs.¹¹ These are surrounded by leukocytes and sometimes by giant cells. The glomeruli are usually spared at first. There may also be metastatic calcification of the kidneys due to hypercalcemia and hypercalcuria.

This kidney involvement is manifested early by albuminuria but that is not related to Bence Jones proteinuria which also may be present simultaneously.

The myeloma nephritis may progress to full renal insufficiency with nitrogen retention and loss of the ability of the kidney to concentrate.

Treatment. There is no cure for this disease. Its progress is variable. Therefore many therapeutic agents have been credited with at least some temporary effect upon the course of multiple myeloma.

Therapeutic agents used fall into two categories: (1) cytotoxic agents which include radiotherapy, urethan, nitrogen mustard and aminopterin; and (2) those agents which affect hyperglobinemia, including stilbamidine, pentamidine, urethan and such substances as cortisone and ACTH.

Results with the use of cytotoxic agents may be summed up as follows:

1. Radiotherapy had been reported to relieve pain and pressure symptoms such as paralysis from a localized lesion. It is of no proved value in diffuse disease. It has produced neither cures nor long lasting remission.

2. Urethan is probably the best chemotherapeutic agent at this writing. Its value rests in its cytotoxic effect as well as its effect on the elevated blood globulin.

Major side effects from urethan are local gastro-intestinal symptoms and systemic ones. The gastro-intestinal symptoms are

nausea and vomiting which may be so severe that an adequate amount of the drug cannot be ingested. Furthermore nausea and vomiting may be just as severe after parenteral administration.

The systemic effects are due to the cytotoxic properties which include liver damage and depression of bone marrow resulting in leukopenia and thrombocytopenia.

The effective dosage of urethan is 2 to 5 Gm. daily until a total of 240 to 300 Gm. has been reached.²¹ When this has been effective in temporarily staying the disease one may actually find decrease of myeloma cells in the marrow, reduction of hyperglobulinemia and restoration of the electrophoretic pattern to normal (abnormal globulins tend to disappear).

Some patients on urethan show calcification of the bone lesions with an elevation of alkaline phosphatase.

The second group of agents affects hyperglobulinemia and includes urethan which was discussed above and which appears to have a dual role.

Stilbamidine and pentamidine were used originally in the treatment of kala-azar. Hyperglobulinemia is constant in this disease. Hyperglobulinemia is also frequent in multiple myeloma. Snapper²² therefore felt that since these chemicals had an effect upon kala azar they also might have an effect upon multiple myeloma. These chemicals were demonstrated to combine with ribose nucleic acid in both myelomatous cells and other body cells.²³ They also have been reported to reduce bone pain. Still, it has not been demonstrated that these substances have any effect upon the inexorable downward course of the disease. Even its original postulated effect upon elevated serum globulin is questionable.

Adrenocorticotrophic hormone and cortisone have been disappointing despite early

favorable reports.²⁴ These compounds produce some subjective relief of pain and improvement in nutrition. Euphoria often associated with the effect of these hormones may be responsible for some of the subjective relief. No consistent suppression of myeloma-cell proliferation or persistent influence upon the abnormal serum proteins has been reported. Bone healing has not been noted.

In view of the fact that no curative modality of treatment is known and that some of the more effective agents may have very distressing side effects the authors are of the opinion that treatment should not necessarily be instituted at the discovery of the disease. When the symptoms warrant however therapy may be employed at the discretion of the physician who should be aware of the dangers involved and the limitations of the therapy considered. The value of commonly employed analgesics for relief of pain is not to be overlooked.

Certain complications of multiple myeloma are amenable to treatment usually surgically. Examples are (1) paraplegia for which laminectomy often combined with radiotherapy is effective and (2) pathologic fractures actual or impending in the shafts of long bones.²⁴

Intramedullary nailing provides a surprising degree of relief and aids in maintaining function. Furthermore actual healing of the fracture may occur.

It should never be forgotten that the intelligent use of braces and plaster for support gives much relief. These are particularly useful in areas such as the spine which are not suitable for intramedullary fixation.

Plates and screws are not advisable because they cannot obtain adequate fixation.

Prognosis. At present the prognosis is hopeless.

TABLE 8 DIFFERENTIAL DIAGNOSIS

[408]

ETIOLOGY		CLINICAL		CHEMICAL	X RAY
Hyperparathyroidism, primary	Hyperplasia or hypersecretion of parathyroids	Nephrocalcinosis Skeletal absorption and deformity Hypercalcemic symptoms		Low serum phosphorus, high serum calcium Marked hypercalcaemia and hyperphosphaturia Elevated alkaline phosphatase Balance studies show negative balance of calcium and phosphorus with greater loss through urine.	Skeletal decalcification Scattered small cysts. Osteosclerotic, with and without calcified trabeculae Ground-glass appearance of skull. Pathologic fractures, deformities Soft-tissue calcifications
Hyperparathyroidism, secondary	Kidney disease producing secondary hyperparathyroidism	Adults — Indistinguishable from above Children — superimposed renal rickets and dwarfism	Adults — Indistinguishable from above Children — superimposed renal rickets and dwarfism	High blood phosphorus. Normal or moderately lowered blood calcium Anemia Balance studies show negative balance of calcium and phosphorus with greater loss through stool. Elevated alkaline phosphatase. Albuminuria, acidosis, low CO ₂ . Low serum ammonium High serum chloride	Same as above
Osteitis deformans (Paget's disease)	Unknown	Bone deformity Skull enlargement. Osteolytic change in bone followed by osteoblastic reaction. Kidney stones	Bone deformity Skull enlargement. Osteolytic change in bone followed by osteoblastic reaction. Kidney stones	Elevated alkaline phosphatase; tendency especially in fraction or bed test for elevated serum calcium with hypercalcaemia Balance studies show retention of calcium and phosphorus. Loss of sulfur and magnesium	Osteolytic advancing wedge followed by osteoblastic reaction. Dense trabeculae. Diffuse in volvement. Enlargement of involved bones Numerous microfractures causing pain and deformity Pathologic fractures of transverse type
Osteomalacia	Defect in vitamin D supply and/or calcium and phosphorus in adults	Skeletal decalcification, fracture and tendency to deformity	Skeletal decalcification, fracture and tendency to deformity	Normal serum calcium Phosphorus occasionally slightly elevated. Elevated serum alkaline phosphatase negative calcium and phosphorus balance	Skeletal decalcification, pathologic fracture, no cysts or tumors. Lower lines (symmetrical periosteal fractures)

Decreased density of the epiphyseal centers occur and eventually generalized decalcification = arakification of bone in very severe form may be seen

Usually unilateral involvement. Some bowing of in older bone with cysts No expansion of center by large cyst

Shepherd crook deformity of hip

Marked absorption of bone structure change more marked in spine "codfish" vertebrae Bilateral compression in lumbar region usually with flattening of the lumbar area and wedge compression in the dorsal spine

Marked thinning of compact layer of bones Poor bone trabeculae

Picture varies from no change in bone to multiple punched-out areas involving all bones. No reaction about margins of lesions.

Pathologic fracture not uncommon

Pathologic fracture common. Marked irregular destruction of bone of osteolytic type—no reaction about edges, except in instance of carcinoma of prostate — that condition shows marked increased bone density

No abnormal chemistry

Café-au lait spots. Tendency to unilateral involvement. Deformity especially of hip. Pathologic fracture

Lowered urinary excretion of twines negative except for the calcium and phosphorus balance
Gentle firm may show lowered urinary 17 ketosteroids, due to decreased adrenal androgen function

Blood cellular changes Elevated calcium.
Reversal A/G ratio high plasma protein. Hence Jones proteinuria

May have elevated serum calcium.
In carcinoma of prostate alkaline and acid phosphatase are elevated

Bone absorption — chiefly of matrix. Observed in older people especially women. Pain in back, vertebral changes

Generalized pain Weight loss, malaise anemia, pathologic fractures, no preceding deformity
Males occasionally have some hypercalcemic symptoms but not usually
Myeloma cells in marrow

Rapid deterioration of patient. Weight loss.
History of primary focus, possible hypercalcemic symptoms

Fibrous dysplasia

Mesenchymal defect

Lack of gonadal and adrenal secretions—low of protein matrix

Plasma-cell neoplasm

Neoplasm metastasizing to bone

Multiple myeloma

Chromatoids

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PART THREE

Diagnostic Classification of
Bone Diseases

Diagnostic Classification of Bone Diseases

METHOD OF CLASSIFICATION AND EXPLANATION OF TABLES

So frequently the experienced clinician confounds the neophyte in his field by an accurate diagnosis. It appears as if he instinctively assesses the facts and reaches the proper conclusion. Often it is done so rapidly and so effortlessly that the conclusion is credited to a "hunch." Yet analysis of a "hunch" indicates it to be nothing more mysterious than a rapid survey of facts weighing of possibilities and selection of the logical answer through previously remembered experience. There is no substitute for this experience, but all physicians come to realize the need of proper classification of the diagnostic possibilities bearing upon the problem at hand.

In Part One the authors have covered the basic material that is of value in understanding what makes bone a living organ of the body. Furthermore its relationship to other systems of the body can be inferred from the data there. It becomes obvious from study of this section that bone is anything but an inanimate supporting structure.

In Part Two the authors have listed and discussed the more common derangements of the skeletal system. It will be noted that emphasis has been placed on the embryologic, the physiologic, the biochemical and the pathologic derangements of bone.

Lesions may be solitary, disseminated or generalized. A *solitary lesion* is defined as a single lesion in one bone in the skeleton (This is exemplified by unicameral cyst.) *Disseminated lesions* are interpreted as multiple lesions which may occur in one or

many bones. Usually they would not occur in all bones, but theoretically this could happen. This group shows normal bone between areas of involvement—either normal areas within the given bone or normal areas in adjacent bones. (Examples are Paget's disease and polyostotic fibrous dysplasia.) *Generalized bone disease* indicates involvement of the entire skeleton. It may appear that such a disease process is confined to portions of the skeleton. An example of this is postmenopausal osteoporosis. However, more careful evaluation of relative bone densities of the rest of the skeleton will show proportionate absorption there also.

Another example is hyperparathyroidism. Here again the clinician may be misled by the more striking osteoclastic tumors (so-called cysts) and overlook the generalized osteoclasia.

Similarly rickets may be considered by some as basically an epiphyseal disturbance, but there is a generalized osteomalacia.

The authors emphasize this division into solitary, disseminated and generalized as Albright emphasizes a similar classification. The reason is that proper classification of a lesion makes it relatively simple to determine the studies needed for conclusive diagnosis.

Always the clinical picture comprising symptoms and signs, must be kept in mind. There is never a substitute for a good history and a thorough physical examination. But following this one may be confronted with a bone lesion evident on the x-ray films taken of the site or sites of chief complaint.

Now one should ask: Is this a solitary, well-circumscribed lesion? Is there more than

one lesion and if so, does the bone about the lesion or lesions appear normal or abnormal?

In the first instance the problem becomes one of analyzing that specific lesion. In the second instance it infers disseminated or generalized bone disease. The third and often the most difficult is the problem of whether the disease is generalized or disseminated.

The approach to the diagnosis is upon the basis of x ray and laboratory findings and oftentimes study of pathologic material with due attention to the clinical background. For example cystic areas in the head of the femur of a rheumatoid arthritis are self evident. Conversely a periosteal proliferative reaction over the tibial crest may well be the result of a contusion and the history will save unnecessary studies and anxiety.

The x ray picture is really a reflection of

gross anatomy and pathology of bone. It is of course, a two-dimensional shadow of a three-dimensional structure. The latter point is understood when for example an osteocartilaginous exostosis diagnosed on anteroposterior and lateral projections simulates an enchondroma on a single projection. The reason obviously is that on a single projection this mass would appear to be contained wholly within the substance of the affected bone. The complementary view would show it to be outside the bone.

An x ray picture will show absorption of bone substance and formation of bone substance. Cartilage proliferation on the contrary unless calcified is radiolucent. Combination of bone absorption or destruction and bone proliferation or bone formative reaction may also be evident roentgenologically.

Therefore listed in the following tables

TABLE 10 DISSEMINATED BONE LESIONS BONE FORMATIVE LESIONS

	BONE PATHOLOGY	ETIOLOGY	BLOOD		URINE	
			Ca	P	Ca	P
Infantile cortical hyperostosis	Osteoblastic	Not known				
Meliorheostosis	Osteoblastic	Developmental				
Metastatic carcinoma of prostate	Osteoblastic	Malignancy	N to +	N to +		
Metastatic carcinoma other than prostate	Osteoblastic	Malignancy	N to +	N		
Multiple osteocartilaginous exostoses	Osteoblastic	Developmental				
Myositis ossificans progressiva	Osteoblastic	Developmental	N	N	Slightly	Slightly
Osteomyelitis	Osteoblastic in subacute phase	Infecting organism				
Osteopathia striata	Osteoblastic	Developmental				
Osteopetrosis	Osteoblastic	Developmental				
Paget's disease	Osteoblastic	Reaction to osteolytic process	N to +	N to +	-	-
Pulmonary hypertrophic osteoarthropathy	Osteoblastic	Lung and heart disease				
Syphilis	Osteoblastic at times	<i>Treponema pallidum</i>				

Key N = Normal. + = Increase - = Decrease.

are lesions that on radiologic study are localized disseminated or generalized Each of these in turn is subdivided into bone absorptive bone-formative or mixed lesions In addition for further diagnostic assistance the conditions associated with abnormal levels of serum calcium phosphorus alkaline phosphatase and acid phosphatase have been listed in tabular form.

TABLE 9 LOCALIZED BONE LESIONS

BONE ABSORPTIVE LESIONS

Euchondroma—no chemical changes
Eosinophilic granuloma—no significant chemical changes
Fibrosarcoma—no chemical changes
Giant-cell tumor—no chemical changes
Infection—no chemical changes but may have systemic reaction including leukocytosis
Metastatic fibrous dysplasia—no chemical changes
Nonossifying fibroma—no chemical changes

Osteogenic sarcoma (osteolytic)—no chemical changes
Osteoporosis
Immobolization—no chemical changes
Irradiation—no chemical changes
Posttraumatic—no chemical changes
Ultrasonic—no chemical changes
Paget's disease—osteoporosis circumscripta—no chemical changes or slight elevation of alkaline phosphatase and sedimentation rate
Unicameral cyst—no chemical changes

BONE FORMATIVE LESIONS

Bone islands—no chemical changes
Brodie's abscess—no chemical changes but may have systemic reaction and leukocytosis
Chondrosarcoma—no chemical changes
Enchondroma—no chemical changes
Infection—no chemical changes but may have systemic reaction and leukocytosis
Monostotic fibrous dysplasia—no chemical changes
Osteogenic sarcoma (osteoblastic)—elevation of alkaline phosphatase may be present
Osteoid osteoma—no chemical changes
Unicameral cyst—no chemical changes

TABLE 10. DISSEMINATED BONE LESIONS BONE FORMATIVE LESIONS—(Cont'd)

FECAL Ca	P	ALKALINE PHOSPHATASE	SERUM PROTEIN	CHOLESTEROL	MISCELLANEOUS
					May have systemic reaction, including fever and leukocytosis
		++	N to —		Acid phosphatase elevated
		N to +			
					Malignant supervision may occur
Slightly —	Slightly —	N			May have fever and leukocytosis
					Systemic reaction and leukocytosis
—	—	++++	N	N	Retained magnesium, calcium and phosphorus Loss of sulfur
					Cyanosis
					Positive serology in many cases

TABLE 11 DISSEMINATED BONE LESIONS BONE ABSORPTIVE LESIONS

	BONE PATHOLOGY	ETIOLOGY	BLOOD		URINE	
			CA	P	CA	P
Blastomycosis	Osteolytic	<i>Blastomyces dermatitidis</i>				
Boeck's sarcoid	Osteolytic	Granuloma	N to +	N	+	N
Brucellosis	Osteolytic	<i>Brucella</i> organism				
Eosinophilic granuloma	Osteolytic	Lipoid granuloma				
Gaucher's disease	Osteolytic	Metabolic				
Gout	Osteolytic	Metabolic				
Granuloma inguinale	Osteolytic	<i>Donovan's granulomatis</i>				
Hand Christian-Schüller's disease	Osteolytic	Lipoid granuloma				
Letterer-Siwe disease	Osteolytic	Lipoid granuloma				
Leukemias	Osteolytic	Malignancy				
Malignant lymphomas	Osteolytic	Malignancy				
Metastatic carcinoma	Osteolytic	Malignancy	+	N	+	+
Multiple enchondromatosis	Osteolytic	Developmental				
Multiple myeloma	Osteolytic	Malignancy	N to ++	N	+	+
Neurofibromatosis (von Recklinghausen)	Osteolytic	Developmental				
Niemann-Pick disease	Osteolytic	Metabolic				
Paget's disease, osteolytic phase	Osteolytic	Unknown	N to +	N to -	N to +	N to +
Polyostotic fibrous dysplasia	Osteolytic	Developmental defect				
Tuberculosis	Osteolytic	<i>Mycobacterium tuberculosis</i>				

TABLE II DISSEMINATED BONE LESIONS BONE ABSORPTIVE LESIONS—(Cont d)

FECAL Ca	P	ALKALINE PHOSPHATASE	SERUM PROTEIN	CHOLESTEROL	MISCELLANEOUS
			N to —		
		+	++		Negative tuberculin test
			N to +		Agglutination and skin tests
				N to +	May have systemic reaction, including fever and leukocytosis
					Large spleen, deposits of cerebroside keratin
					Uric acid increase
					Donovan body
				N	Diabetes insipidus, ex ophthalmos and skull changes
				N	Severe usually fatal, systemic reaction
					Peripheral blood and marrow findings
		+ at times			Lymph nodes
N	N	N to ++			Malignant supervention may occur
N	N		+ to +++++		Bence Jones proteinuria present in 60% of cases
					Deposits of phospholipids, chiefly lecithin and sphingomyelin
N	N	N to +			Loss of magnesium, calcium and phosphorus
			N to —		Tuberculin test

TABLE 12 DISSEMINATED BONE LESIONS MIXED LESIONS

	BONE PATHOLOGY	ETIOLOGY	BLOOD		URINE	
			Ca	P	Ca	P
Congenital hemolytic jaundice	Similar to Mediterranean anemia (q.v.) but to lesser degree	Congenital anomaly of red cells				
Leukemias	Osteolytic and osteoblastic	Malignancy				
Malignant lymphomas	Osteolytic and osteoblastic	Malignancy				
Mediterranean anemia (Cooley's anemia)	Proliferation of bone marrow distention and proliferation of cortex, so mixed bone absorption and bone formation occur	Congenital anomaly of red cells				
Metastatic carcinoma of prostate	Osteoblastic and osteolytic	Malignancy	N to +	N to +		
Metastatic carcinoma other than prostate	Osteoblastic and osteolytic	Malignancy	N to +	N	+	+
Paget's disease	Osteoblastic and osteolytic	Reaction to osteolytic process	N to +	N to +	-	-
Polycystotic fibrous dysplasia	Osteolytic and osteoblastic	Developmental defect				
Sickle-cell anemia	Similar to Mediterranean anemia (q.v.) but to lesser degree. Aseptic necrosis from thromboses	Congenital anomaly of red cells				

TABLE 13 GENERALIZED DISEASES OF BONE BONE FORMATIVE LESIONS

	BONE PATHOLOGY	ETIOLOGY	BLOOD		URINE	
			Ca	P	Ca	P
Hypervitaminosis A	Osteoblastic	Excess vitamin A				
Hypervitaminosis D	Osteoblastic	Excess vitamin D	+	+ or -	+	+
Hypoparathyroidism	Osteoblastic	Lack of parathyroid hormone	--	++	--	--
Hypothyroidism	Possible osteoblastic	Lack of thyroid function				
Osteopetrosis	Osteoblastic	Developmental				
Pseudohypoparathyroidism	Osteoblastic	Unknown	--	++	--	-
Scurvy	Osteoblastic	Lack of ascorbic acid				

TABLE 12 DISSEMINATED BONE LESIONS MIXED LESIONS—(Cont'd)

FECAL Ca	P	ALKALINE PHOSPHATASE	SERUM PROTEIN	CHOLESTEROL	MISCELLANEOUS
					Increased red-cell fragility
					Bone marrow and peripheral blood studies
		+			
					Target red cells Bone marrow studies. Red cells have decreased fragility
		++	N to —		Acid phosphatase elevated
		N to +			
N to —	N to —	++++			Retained magnesium Loss of sulfur
		N to +			
					Sickling test

TABLE 13 GENERALIZED DISEASES OF BONE BONE FORMATIVE LESIONS—(Cont'd)

FECAL Ca	P	ALKALINE PHOSPHATASE	SERUM PROTEIN	CHOLESTEROL	MISCELLANEOUS
—	N to —				Osteinosis
—	—	N to —			Tetany Trousseau sign + Chvostek sign + Responds to parathyroid hormone and dihydro-tachysterol
				+++	Delayed bone age
					No response to parathyroid hormone
					Low vitamin-C blood and tissue levels

TABLE 14 GENERALIZED DISEASES OF BONE BONE ABSORPTIVE LESIONS

	BONE PATHOLOGY	ETIOLOGY	BLOOD		URINE	
			Ca	P	Ca	P
Acromegaly	Osteoporotic	Pituitary hyperfunction and hypogonadism	N to —	N to +	+	+
Celiac disease	Osteomalacic	Deficient fat absorption	N to —	N to —	—	—
Cushing's syndrome	Osteoporotic	Adrenal S hormone increase, protein not available for bone matrix	N to —	N to +	N to +	N to +
Diabetes	Osteoporotic	Pancreatic dysfunction				
Fanconi's rickets	Osteomalacic	Kidney tubular disease. Amino-acid diabetes. Cystinosis	N to —	—	+	+
Hyperthyroidism	Osteoporotic	Depletes protein for bone	N	N	++	++
Hypervitaminosis D	Osteoclastic	Excess vitamin D	+	+ or —	+	+
Idiopathic steatorrhea	Osteomalacic	Deficient fat absorption	N to —	—	—	—
Immobilization	Osteoporotic	Elimination of stress and strain	N to +		++	N to +
Infantile rickets	Osteomalacic	Vitamin D lack in children	N to — C X P = —	N to —	—	—
Kidney glomerular disease with osteitis fibrosa generalisata	Osteoclastic	Kidney disease. Compensatory hyperparathyroidism	— 5-9	+ 6-10	+	—
Mixed renal disease, secondary hyperparathyroidism, and renal osteitis fibrosa generalisata	Osteoclastic and osteomalacic	Kidney glomerular and tubular disease producing decreased serum calcium and increased serum phosphorus and resulting parathyroid hypersecretion	6-9	6-10	++	—
Osteogenesis imperfecta	Osteoporotic	Developmental				
Osteomalacia	Osteomalacic	Vitamin D lack in adults	N to — C X P = —	N to —	—	—

TABLE 14 CENTRALIZED DISEASE OF BONE BONE ABSORPTIVE LESIONS—(Cont d)

FECAL Ca	P	ALKALINE PHOSPHATASE	SERUM PROTEIN	CHOLESTEROL	MISCELLANEOUS
		N			Negative nitrogen balance
++	++	N to +		N to —	Increased fecal fat content; Increased prothrombin time
		N			High total of 11-oxy steroid in urine
			N to —	++	
++	++	+			Calcinosis. Glycosuria Amino-aciduria
N	N	N to +	N to —	— 130-190	BMIR +++++ Increase of protein-bound iodine Radioactive iodine uptake increased
—	N to —				Calcinosis
++	++	N to +		N to —	Increased fecal fat content. Increased prothrombin time Decreased absorption of fat-soluble vitamins
N	N	N			
++	++	+			
+++	++	+		N +	Calcinosis
++	++				Calcinosis. Signs of glomerular disease usually predominate over tubular form and P diuretics does not occur
					May have associated blue sclerae, joint hyperlaxity and hearing defects
++	++	+			

TABLE 14 GENERALIZED DISEASES OF BONE BONE ABSORPTIVE LESIONS—(Cont'd)

	BONE PATHOLOGY	ETIOLOGY	BLOOD		URINE	
			Ca	P	Ca	P
Postmenopausal osteoporosis and senile osteoporosis	Osteoporotic	Lack of gonad function	N to —	N	N to +	+
Primary hyperparathyroidism (osteitis fibrosa generalisata)	Osteoclastic	Secreting parathyroid adenoma	11-20	1-3	++++	++++
Radiation osteoporosis with fracture	Osteoporotic	Reduction of osteoblastic action by x ray effect				
Scurvy	Osteomalacic		N to —	—	—	—
Tubular osteomalacia and rickets (Albright Butler)	Osteomalacic	Kidney tubular disease with loss of fixed base	—	—	+	+
Vitamin D resistant rickets	Osteomalacic	Resistance to vitamin D effect	N to — C × P = —	—	—	—

TABLE 15 GENERALIZED DISEASES OF BONE MIXED LESIONS

Hyperparathyroidism
Scurvy
Healing phases of
Osteomalacia and rickets
Osteoporosis

TABLE 16 ELEVATED SERUM CALCIUM

Normal levels	9 to 11 mg. %
Occurs in	
1 Hyperparathyroidism	13 to 20 mg. %
a. Primary	
b. Secondary	
2 Low phosphorus rickets and osteomalacia	11 to 13 mg. %
3 Hypervitaminosis	11 to 15 mg. %
4 Osteogenic sarcoma	11 to 14 mg. %
5 Multiple myeloma	14 to 15 mg. %
6 Metastatic carcinoma	11 to 15 mg. %

TABLE 17 LOWERED SERUM CALCIUM

Normal levels	9 to 11 mg. %
Occurs in	
1 Tetany (parathyroid)	6 to 8 mg. %
2 Hypoparathyroid states	6 to 8 mg. %
3 Renal glomerular disease	8 to 10 mg. %
4 Renal tubular rickets or osteomalacia	6 to 10 mg. %
5 Postmenopausal or senile bone osteoporosis	8 to 10 mg. %

TABLE 18 ELEVATED SERUM PHOSPHORUS

Normal levels	
1 Infants	5 to 6 mg. %
2 Children	4 to 5 mg. %
3 Adults	3 to 4.5 mg. %
Occurs in	
1 Kidney dysfunction	
a. Congenital malformation	may reach 6 to 10 mg. %
b. Glomerular disease	
Slight elevation may occur in	
1 Secondary hyperparathyroidism	
2 Postmenopausal osteoporosis	
3 Senile bone osteoporosis	
4 Acromegaly	
5 Hypoparathyroid states	

TABLE 19 LOWERED SERUM PHOSPHORUS

Normal levels	
1 Infants	5 to 6 mg. %
2 Children	4 to 5 mg. %
3 Adults	3 to 4.5 mg. %
Occurs in	
1 Hyperparathyroidism—may be as low as 1.1 mg. %	
2 Rickets	} due to decreased vitamin D cal- cium and phosphorus intake
3 Osteomalacia	

TABLE 14 GENERALIZED DISEASES OF BONE BONE ABSORPTIVE LESIONS—(Cont d)

FECAL Ca	P	ALKALINE PHOSPHATASE	SERUM PROTEIN	CHOLESTEROL	MISCELLANEOUS
++	+	N to —			Decreased 17 ketosteroid output
+	N	20-15			Protein loss
++	++	N to +		N to —	Increased fecal fat in increased prothrombin
+	+	+			Calcinosis <i>Acidosis</i> Loss of ability to make ammonia in tubules
++	++	+			Massive vitamin D dosage necessary for treatment

TABLE 20. ALKALINE PHOSPHATASE

Normal level	
Bohannon units	2.5 to 4 (adult) 1.5 to 1.5 (children)
Elevated in	
1. Paget's disease	25 to 100
2. Hyperparathyroidism	20 to 35
a. Primary	
b. Secondary	
3. Carcinoma of the prostate with metastases	about 25
4. Osteogenic sarcoma	15 to 40
5. Obstructive liver disease	25 to 100
Normal levels are too low for a decrease to be significant	

TABLE 21 ACID PHOSPHATASE

Normal levels	
Bohannon units	0.1-0.8
Elevation occurs in	
1. Carcinoma of the prostate with bone metastases	may go to 125 B U
Values between 0.5 and 1.0 B U are suggestive of osseous prostatic metastases	

TABLE 22 BLOOD CHOLESTEROL

Normal level	115 to 300 mg %
Elevated in	
1. Renal nephrosis	up to 1,000
2. Hypothyroidism	up to 400
3. Diabetes	up to 2,000
4. Reticuloendotheliosis	
Usually normal	arely elevated
a. Hand Christian Schüller	

b. Letterer-Siwe	
c. Eosinophilic granuloma	
5. Biliary obstruction	up to 4,400
6. Liver disease	500 to 600
Decreased in	
1. Hyperthyroidism	130 to 190
a. Diagnosis confirmed by bone age, BMR and protein-bound iodine	
2. Terminal kidney disease	
3. Advanced bone disease	
4. Pernicious anemia	
5. Failing metabolism in generalized renal and biliary disease	

TABLE 23 BALANCE STUDIES RETENTION OF PHOSPHORUS AND CALCIUM

Occurs in	
1. Hyperostotic or eburnated phase of Paget's disease	
2. Renal conditions	
3. Hypoparathyroidism	

TABLE 24 BALANCE STUDIES LOSS OF PHOSPHORUS AND CALCIUM

Occurs in	
1. Primary hyperparathyroidism	
2. Osteoporotic processes after operation and immobilization	
3. Postmenopausal and senile osteoporosis	
4. Cushing's syndrome with osteoporosis	
5. Hyperthyroidism	
6. Severe diabetes	
7. Metastatic carcinoma	
8. Multiple myeloma	

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